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BRITISH MEDICAL JOURNAL

LONDON SATURDAY DECEMBER 12 1953

# VITAL STATISTICS AND THE DOCTOR*

BY

**Sir RUSSELL BRAIN, D.M., P.R.C.P.**

*Physician to the London Hospital and the Maida Vale Hospital for Nervous Diseases*

The opportunity of being present on a historic occasion does not come very often, but I believe that the date of this First International Congress on Health and Vital Statistics promoted by the World Health Organization will be remembered as one which saw the first embodiment in form and action of a new idea which is to prove of the utmost importance for the future of medicine and, indeed, I can say without exaggeration, of mankind. I call it a new idea, but perhaps it would be not inappropriate to speak of it as a new conception, for it is no mere chance that in English we use the same word to describe both the birth of an idea and the origin of a new life. Human societies, whatever else they may be, are certainly biological organizations. Philosophers spend a good deal of time to-day discussing the body–mind relationship, but they nearly always mean by that the relationship between one particular mind and the body with which it is associated. Sociologists, however, and others who concern themselves with the ideas which move and change societies are equally dealing with an aspect of the body–mind relationship, for it is certain that new ideas can influence society only in so far as they are embodied in its individual members. So when I speak of this meeting as being in a double sense a conception, I am speaking not metaphorically but literally. The new human individual possesses only two parents, but social structures are more complex in certain respects, and to-day a new idea has been brought to birth owing to the vision and enthusiasm of workers in many countries in all parts of the world.

### A Biological Event

This, let me say again, is not a mere fantasy, but a strictly biological account of a biological event, for we are living in an era at which life has reached one of the critical stages of its evolution, when, for a variety of reasons, national organizations have come to see that they are not self-sufficient and when new organizations are developing which seek to operate as a mode of intelligence for the whole of mankind.

It is appropriate that medicine should be in the forefront of this process. The aims of medicine are purely beneficent, and it is our proud and treasured tradition that medical science knows no national boundaries and that a discovery made in one country to-day is available to the rest of the world to-morrow. But there is another, and even more important, reason—namely, that the conditions of health of each single individual are profoundly modified by the fact that he or she lives in a community, and in this respect to-day the world is a single community. Infection can now spread in a few days from one end of the world to the other, and may thus enter a country in which, as a result of their bacteriological history, the inhabitants possess a poor immunity to the invader. Hence every nation is vitally interested in the incidence of many infections in all other nations. Moreover, differences in the morbidity and mortality statistics for different diseases in different parts of the world may prove of the greatest value in providing clues to their causation: cancer is one obvious example of this. From a broader standpoint population trends, which constitute one of the most important factors that have to be taken into account by international statesmanship to-day, require accurate statistics for their calculation.

### Importance of Vital Statistics

These, of course, are familiar facts, and we shall not be disposed to underestimate the difficulties which face us when we seek to make our governments, our medical professions, and, indeed, the public in general more aware of the importance of vital statistics, of the need for uniformity in this field, and of the fundamental necessity for accuracy in the data. Let me briefly consider these questions in their reverse order.

It is obvious that the causes to which death is attributed must fall far short of complete accuracy in all countries. A post-mortem examination is nowhere performed in more than a small proportion of cases, and even that may need to be supplemented—for example, by bacteriological studies. Accuracy should be improved as more and better diagnostic methods become available, and particularly as members of the medical profession are educated to realize the importance of vital statistics. The confidentiality of information acquired by a doctor about his patient constitutes a genuine problem. Wide differences in this respect exist between different countries. In this country the medical profession, with the encouragement of the Royal Colleges, has felt free for over a century to report the cause of death upon a certificate which becomes available to the general public. I am sure that progress in this sphere will be made only by taking full account of the feelings of the profession in different countries and discussing what safeguards it is possible to introduce. Full safeguards are likely in themselves to increase the accuracy of the records.

The need for uniformity needs no emphasis. But how far is it practicable to go in this direction? Perhaps a wise policy for the time being is to aim at obtaining uniformity in a comparatively small field rather than to attempt more than it is at present practicable to achieve.

It is rather widely believed that vital statistics are dull; and it is important that we should succeed in dispelling this idea. I have often reflected on the fact that preventive medicine seems somehow to lack glamour. The novelist or

*Presidential address to the First World Health Organization International Congress on Health and Vital Statistics, October 12, 1953.

the author of a film scenario may show you the great surgeon peeling off his rubber gloves after removing the appendix, or the psychiatrist administering to his patient an electric shock, but somehow he does not find romance in the medical officer of health bringing a typhoid epidemic to an end, or in the vital statistician studying the number of deaths from carcinoma of the lung.

It is of fundamental importance to arouse or increase the interest of governments, doctors, and the public in all countries in vital statistics, for without this better technical methods by themselves can achieve little. It is undeniable that at present neither vital statistics nor even public health and preventive medicine excite the interest which their importance deserves and needs, and if we are to change the public attitude to them we must first try to discover why this is so.

### Attitude Towards Preventive Medicine

Let us consider first the attitude of the medical profession, since in a sense the doctors are the key to the situation, partly because their direct help is essential, and partly because they are the natural propagandists for preventive medicine, with unique opportunities of obtaining the ear both of peoples and of governments. It might be thought that doctors who spend their lives dealing with the results of disease could be equally active in the sphere of preventive medicine, yet experience shows that this is not necessarily the case. It has to be remembered, first, that doctors who devote themselves chiefly to treatment usually have little time for much else; and, secondly, that the man or woman who is by temperament attracted to the practice of medicine with its concrete problems and personal relationships, though daily made aware of the importance of preventive medicine, is usually less interested in and fitted for what seem the more abstract problems of the aetiology and prevention of disease and the administrative measures for which the latter often calls. Conversely, the medical statistician and the medical administrator have chosen their sphere of work in preference to consultant or general practice.

### Co-operation of Statistician and Physician

Hughlings Jackson quoted Herbert Spencer as saying that integration must keep pace with differentiation as division of labour necessitates co-operation, and nowhere is this truer than in preventive medicine. The statistician and the physician are not doing different jobs; they are dealing with different but inseparable aspects of the same job. Let me illustrate this by reference to poliomyelitis. It is a commonplace which is too easily forgotten that clinical observation is the foundation of all knowledge, for the nosological isolation of a disease depends in the first instance almost always upon a combination of clinical and pathological observation; and bacteriology and immunology are built upon the same twin foundations. But when we come to the practical fieldwork of epidemiology clinical recognition of paralytic and, still more, of abortive cases is basic. All this is perhaps obvious, but I stress it because I believe it points the way to increasing the interest of the clinician in vital statistics, which is to convince him that his contribution, just as in preventive medicine generally, must be made, not to what is apt to seem to him an obscure and abstract discipline, but in his own sphere, in which he is the specialist, and where the part he has to play is indispensable because it is irreplaceable.

That is what I meant by saying that the clinician and the statistician deal with different but inseparable aspects of the same job. The statistician depends on the clinician for the accuracy of his data, whether these be diagnoses of disease during life or causes of death, and upon the accuracy of these data his whole work depends. But the statistician is not using statistics for their own sake, but in order that the conclusions which he draws from them may be applied in practice, and in the practice not merely, perhaps not chiefly, of the administrator, but also of the general practitioner and consultant. The relationship between the statistician and the clinician is thus a symbiosis, and nothing would better arouse the interest of the clinician than information which would convince him of the value to himself of the material which he supplies.

### A Great Achievement

Vital statistics dull! Not myself a mathematician, perhaps I can afford to romanticize mathematics a little. It was Pythagoras who set number at the heart of the universe and saw in mathematical relations the foundation of everything that exists. I have often thought that the present age might fitly be described as Neo-pythagorean. Every branch of science has become increasingly dependent upon mathematics, and future historians of thought may well regard it as the supreme achievement of the human mind that it was able to create mathematical symbols of such complexity and subtlety as to provide what seems to be an inexhaustible mode of representing the universe, for on this symbolic representation depends in no small degree our power of action. It is surely of particular interest to us to-day that, if I understand them aright, mathematical physicists have found that when they seek to represent the behaviour of matter in its minutest subdivisions only statistical methods are applicable. And it is to the mathematics of statistics applied to human populations that we look for the source of our power to improve health and prevent diseases which cannot be controlled in any other way. This congress therefore has a twofold purpose—that we may learn from each other, and that we may collectively impress upon the widest possible public the importance for the welfare of the whole world of the task upon which experts in vital statistics are engaged.

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## SAMPLING IN MEDICAL RESEARCH

BY

**COLIN WHITE, M.B., M.Sc.**

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A hint that the importance of sampling has not been sufficiently recognized in medical work may be found in the common use of the word "specimen" at times when it would be more helpful to refer to a "sample." The former term tends to imply that one can rely on the material under examination, in the way a botanist usually does when classifying a plant; and that, if mistakes are made, they arise not because the material is atypical but rather because the knowledge of the examiner is imperfect. On the other hand, to use the word "sample" is to remind oneself of the widely recognized fact that samples may be good or bad, fair or biased, representative or misleading; and that all sampling entails, therefore, a sampling error, which is just as great a hazard for the professor or consultant as for the junior assistant.

To emphasize this hazard it may be helpful to examine a few cases in which the results of some experiment or survey have been affected by biased sampling. In the first three examples the bias was important enough to invalidate the conclusions.

### Examples of Biased Sampling

Keys *et al.* (1947) have given a lively description of a common error regarding the effect of starvation on the weights of various organs and tissues. It is claimed in many textbooks that when an adult animal is starved the decrease in the weight of the heart is relatively much smaller than the decrease in the weight of the voluntary muscles. This idea arose from a commentator's account of some work by

C. Voit in which two cats, one starved and one well-fed, were used in an experiment. The details given in the original account of the work included the weights of certain organs and tissues in the two animals; and it is easy to calculate from these that, if the well-fed animal is regarded as a control, starvation in one particular cat reduced the weight of the heart by only 2.6% and the weight of the voluntary muscles by as much as 30.5%. Voit did not discuss this point, because it was merely incidental to his problem, but the figures were later picked out by others and illustrated by clear diagrams. Next a mechanism was described to explain how the heart could be maintained on the decomposition products of other tissues. Finally, it was emphasized how easily the results could be reconciled with the philosophical view that this was one more example of the wisdom of the body in maintaining the most important organs. It is difficult to find a medical student to-day who is unaware of these matters, because the story is so interesting and reasonable that it is easy to tell and easy to remember. Unfortunately, it is not true, for at least one of the two cats was atypical, so far as the weights of the organs were concerned. The sample was misleading.

The next example is from the field of public health. At the beginning of this century it was widely believed in Britain that the population was deteriorating in physique. Public opinion had been stirred by the claim that of every five men offering for enlistment in the Army only two were found effective soldiers after the lapse of two years. A committee was set up by the Privy Council to consider this problem. It stated (Report, 1904) that there was little evidence of progressive physical deterioration, but that the men offering for enlistment at that time were not representative of the people as a whole: they were, in fact, a biased sample, with average physique poorer than that of the population from which they were drawn.

The third example is a large-scale experiment on nutrition—the Lanarkshire milk experiment—which was carried out in 1930 and has been summarized and criticized by Student (1931). Over a period of four months 5,000 schoolchildren received ⅓ pint (425 ml.) of raw milk a day and a further 5,000 received the same amount of pasteurized milk. Another 10,000 children acted as controls. The whole 20,000 had their height and weight measured at the beginning and end of the investigation. It was an experiment planned on a grand scale and carried through with skill and industry; but, unfortunately, the methods of sampling were not rigorous enough. In the first place, the teachers were given some freedom of choice in allotting the children to the control or experimental group; and they exercised it by including too high a proportion of ill-nourished children among those who took milk. A second defect was that each school receiving milk was given either raw or pasteurized, so that the two kinds of milk were not tried out on different pupils from the same school; and, since the experiment was restricted to 67 schools drawn from a rather heterogeneous area, it is quite possible that the group of children drinking raw milk was not comparable to that receiving pasteurized.

In criticizing this experiment we have to remember that in 1930 detailed knowledge of the technique of sampling human populations was confined to relatively few experts. There were no books available on the subject of sampling, and the periodical literature was scanty and rather inaccessible. Moreover, faith in the reliability of large samples was so general among medical workers as to seem almost an unofficial extension of the Hippocratic Oath. But, acknowledging these difficulties, we still have to regard the experiment as a huge waste of effort, and as a warning to future workers of the danger of biased sampling.

In the following example there was no deliberate attempt to select a sample at all; but, in the course of work at a laboratory in Baltimore, Rh-typing was carried out on many people, and it might have been reasonable to suppose that, as the data accumulated, a more and more reliable sample of the population was being obtained. Glass (1950) noticed, however, that of the first 5,000 white subjects examined 15.6% were Rh-negative, but by the time 28,000 subjects had been examined the Rh-negative group had increased to 17.7%. This difference is large, and it is clear that those typed were not a consistently fair sample of the population from whom they were drawn. There was no reason why this biased sampling should have been expected, but bias is so often unexpected that it is wise to take routine precautions against it, if possible, whenever a sample is drawn. Many observers would think it unnecessary to carry out the sort of analysis undertaken by Glass, and would be surprised to find similar bias in their own data.

### Random Sampling

The simplest precaution against bias in sampling is to take the sample at random, and, in the absence of background knowledge about the population, we cannot do better than this. It is true that the error involved in random sampling may be rather large; but the important advantages are that the sample itself provides a valid estimate of this error, and that the error can be reduced, if necessary, by increasing the number of cases. Random sampling is a strict process of selection, which is roughly equivalent to drawing lots, and which ensures that each member of the population has the same probability of being selected. Unfortunately, it is difficult to carry out; in fact, the random sample is a theoretical concept which never finds its exact counterpart in the world around us; for even the tossing of coins and the rolling of dice are only close approximations to random sampling.

The methods used for drawing samples in medical research usually fall far below these standards; there is often a factor of expediency involved—for example, when the items required are obtained from a relatively small, and conveniently accessible, part of the whole population. In such a case the risk is clear, but at other times the problems may be subtle as well as serious, for, as Feller (1950) has written, "In sampling human populations, the statistician encounters considerable and often unpredictable difficulties, and bitter experience has shown that it is difficult to obtain even a crude image of randomness." Nevertheless, in such an important matter it is worth while defining the objectives and describing some common dangers.

As a first step the investigator should review the sampling process before the collection of data is begun, and should satisfy himself that there is no obvious source of error. This review must be penetrating: it is not enough to have a clear conscience about the sampling, because we may have this even when the subconscious is anything but clear; moreover, it is not enough to argue that the sampling is haphazard, because the definition of what is haphazard varies with our understanding of the problem, and we may err through ignorance; or, again, it is far too optimistic to hope that we will obtain a random sample merely because we can identify certain sources of bias, of which some are likely to work in one direction and some in the other. The ideal precaution to take is to ensure that the observer has no freedom of choice in selecting the sample. This is a job in which human beings can hardly be trusted: once the observer is allowed an element of personal choice the selection of the sample is likely to be influenced by the qualities of the objects sampled, and the element of randomness is jeopardized. One procedure which is often feasible in a well-planned experiment or survey is to number the population to be sampled and then use a table of random numbers to determine which members will be selected. The practical details of this method, and various alternative methods, are described by Yates (1949).

Sometimes an investigator, through no fault of his own, may have been unable to obtain a random sample, but he may be familiar with the material under study, and have a clear idea of the type of sampling process that has been used. In this case it may be reasonable to define a population, if necessary a hypothetical one, such that the sample can be regarded as having been drawn at random from this population—for example, certain results obtained in a

survey may not apply to children in general, but may be true of a population which one could define roughly as healthy children; the concept of such a class is perhaps rather vague but may seem adequate for a particular problem. Another example is provided by the report of Kinsey *et al.* (1948) on the sex life of the male. It is clear that the results obtained by these workers are not valid for the male population of the United States as a whole, because there is excessive weighting of certain groups, such as college students, residents in and around Indiana, and people with a professional interest in Kinsey's novel methods of interviewing. Nevertheless the subjects examined may perhaps be considered a random sample from some population that would still be of great interest. In this imaginary construction of populations, however, we should bear in mind the acid comment that certain samples are representative only of themselves.

### Probability Sampling

Simple random sampling is the best known of a group of unbiased methods that are described collectively as probability sampling. The essential characteristic of these is that each item in the population has a known probability of being selected for the sample, and, as a result of this, valid errors can be calculated for the estimates made from the data. Descriptions of various types of probability sampling have been given by Yates (1949) and by Deming (1950). One example is stratified sampling. If we attempted to investigate the haemoglobin level of adults in a particular city by simply taking a sample at random, we could not define the value very closely unless we examined a large number of cases. The method would not be misleading, but it would be tedious if accurate information were needed. We could obtain a better estimate from fewer examinations if we stratified the population into groups according to criteria, such as age and sex, which are known to affect haemoglobin values, and then drew a random sample from each of the various strata. The method of stratified random sampling enables us to use background information efficiently. Since some information of this kind is almost always available to those who carry out large-scale surveys, it is rare to find such people using simple random sampling. The latter method is commoner in laboratory work, but is not always used; in fact, the large literature on what is called, perhaps somewhat misleadingly, the design of experiments is simply an account of various methods of sampling.

The advantages of employing some form of probability sampling are considerable. It is true that if we draw non-random samples we may select a group of items which represent the population very well, especially in respect of some quantity such as mean value on which we have deliberately concentrated; but there is a disturbing uncertainty in our conclusions, for we have no objective way of assessing the error made: the usual statistical methods do not apply when the samples are non-random. Of course, any sample at all yields some information about the universe from which it is drawn, but only in the case of probability sampling can the information be assessed in terms of the theory of statistics. This limited value of non-random samples has important effects on scientific procedure—for example, it is wrong to believe that you have only to increase the size of a sample enough in order to be able to draw powerful conclusions. Quality, in general, is more important than quantity; if the sampling is biased an increase in the number of individuals may merely commit you more and more firmly to a false hypothesis. It also follows that when authors are in disagreement the one with the larger number of cases is not necessarily correct.

### Other Types of Sampling

A good case can often be made out for using methods of sampling which are known to be biased. Several instances of this occur in the process of measurement, which, in the present context, may be regarded as a method of sampling. If the bias is constant and can be assessed, then it may simply be subtracted from the end-result, like a biochemist's correction for the blank. If the interest lies in the difference between two measurements, the same amount of bias may enter into each without affecting the results at all. Again, it may be possible to calibrate a biased method against an accurate method, and thereafter use the former, on the ground that it is cheaper, quicker, more convenient, or more likely to give reproducible results—for example, the measurement of the carbon dioxide percentage in "alveolar air" by using end-expiratory samples has the last three of these advantages. Finally, in a given problem the bias of a customary technique may be unimportant. It is fortunate when this is so, for the virtual elimination of bias in measurement—that is, the determination of absolute values—involves the most painstaking care, and often requires facilities that are available in only a few special laboratories.

Another type of biased sampling, in which some expert takes the responsibility of picking the items, has been described by Deming (1950) as judgment sampling. It would be risky to endorse such a method freely, but it is nevertheless common and important in medical research, and is especially useful in the pioneering phase of a problem. The more objective methods can be used when some promising ideas have been developed.

Perhaps the clearest statement of the role of judgment sampling in experimental medicine has been made by Claude Bernard (1865). In a discussion of the method of reporting the results of a group of experiments in which there had been some variations in conditions and techniques, he warned against any attempt to combine the details of several experiments into a kind of average description, and recommended the use of expert judgment: "Quand on a affaire à des expériences complexes et variables, il faut en étudier les diverses circonstances et ensuite donner l'expérience la plus parfaite comme type." A similar idea is expressed in a more colloquial way by the physiologist who inspects the kymograph record and remarks that he has obtained a "publication" tracing.

Judgment samples vary in value according to the ability of the expert; at times this has the unfortunate effect of concentrating attention and debate on the extent of this ability. There is, however, an alternative to argument directed at the men concerned, and that is to regard any conclusions from judgment sampling as tentative until the findings have been checked, preferably by an independent technique.

Quota sampling is a type of judgment sampling which is widely used for commercial and social surveys, but has not, so far, become important in medical work. In this method quotas are allotted to certain important classes—for example, the sample might be planned to contain so many people from the different age groups, so many of each sex, and so many from each social class. Once the quotas have been allotted the interviewers are free to obtain the necessary subjects in whatever way they can. The method may be disastrous, but it does work well at times when the planning is thorough. It has the advantage of cheapness.

### Bias in Hospital Statistics

Suppose an investigator wishes to find out whether vascularization of the cornea seems to be associated with deficiency of riboflavin. In order to obtain enough cases for a satisfactory conclusion he might carry out his research on patients in a hospital. A control group of patients without deficiency of riboflavin might be provided from the same hospital, and perhaps steps would be taken to match the two groups in respect of age, occupation, and any other factor that might be known to influence the incidence of vascularization of the cornea. When the survey had been concluded the investigator would be able to draw up a $2\times2$ table showing how many subjects fell into each of the four possible groups, characterized by one or other abnormality, neither, or both. If the results did not seem clear-cut, perhaps the data would be treated by a standard statistical test such as the chi-squared test.

In an interesting paper Berkson (1946) has shown an important fallacy in this type of argument: his objection to the method can be stated in terms of biased sampling. Consider a population in which there is no association between the sign and the disease under study—that is, the percentage of people with vascularization of the cornea is the same in the deficient group as in the rest of the community. We may now imagine that the patients in certain hospitals are drawn from this community. If the probability that a person entered hospital differed according to whether he was deficient in riboflavin or not and also according to whether he had vascularization of the cornea or not, then the hospital population would not reflect the true incidence of these factors, and would give a false picture of the problem under investigation. The results, however carefully developed, would be an artifact. The true relationship between the two factors would sometimes be stronger and sometimes weaker than that indicated by the sample of hospital patients, for the bias might tend in one direction or the other according to the way the patients were drawn from the four groups in the community.

This is a far-reaching criticism extending, as it does, to many current projects in medical research; but it must be modified in one important respect. Suppose that the presence of duodenal ulcer influences the probability that a person would be admitted to hospital, but the nature of his blood group does not. Then, on these assumptions, the patients in hospital could be used to obtain a valid estimate of any hypothetical association between blood group and the incidence of duodenal ulcer. If the association were zero, for example, then such a state would be reflected in a group of hospital patients just as well as in a group taken from the community. The saving factor here is that, since the blood group is without effect on the probability that a person would enter hospital, the mere concentration in hospital of large numbers of patients with duodenal ulcer would not distort the true relation between the blood group and the disease. Such distortion will not occur unless both of the factors being examined affect the probability of becoming a hospital patient.

The problems raised by the use of hospital statistics may be illustrated clearly by a reference to thromboangiitis obliterans. It used to be accepted that this disease occurs chiefly in Jews; but, more recently, there have been numerous reports that contradict such a view. It is now recalled that Buerger and many of the other early investigators of thromboangiitis obliterans worked at hospitals where the patients were predominantly Jewish; so that the supposed racial predisposition to the disease was an error due to biased hospital statistics.

### Bias in Post-mortem Statistics

The bias to which Berkson has drawn attention in the case of hospital statistics is even more likely to occur when statistics are collected from post-mortem records. The morbid anatomist probably has little to learn from current statistical methods of testing hypotheses, because, in general, his material is necessarily obtained by methods of sampling which invalidate the tests of significance that a statistician employs. An early paper by Stocks (1924) shows that he sensed this point, though he had no method of neutralizing the bias which it might cause, for, as Berkson has pointed out in regard to similar problems of hospital statistics, "There does not appear to be any ready way of correcting the spurious correlation . . . by any device that does not involve the acquisition of data which would themselves answer the primary question."

Post-mortem results may be equally subject to bias when they involve measurements. Marshall (1951) has carried out t-tests to determine whether the heart weight observed after death differs according as the subjects have normal or aberrant renal arteries. If we wish to apply these results to the population in general, however, we have to remember that no care or skill on the part of the pathologist can ensure that he obtains a random sample of material from the general population; his sample is determined by factors over which he has little control. Whenever an investigator is forced to draw his sample, not from the population in which he is interested but from some pre-selected portion of it, he is in danger of obtaining a biased group. In effect there are then two stages of sampling; the investigator controls the second stage, and perhaps carries out his work with scrupulous care; but this may be of no avail if there has been bias in the first stage.

To illustrate this point, suppose that someone takes a random sample of schoolchildren in a certain area and finds out in each case how many there are in the family to which the child belongs. The sampling of the schoolchildren may fulfil all the requirements of random selection, but the data obtained will be biased if they are used to give an estimate of the average number of children per family. It is clear that various families have different chances of being included in the sample; an extreme case is that of the childless family which has zero chance of being selected.

### Fallacy of the Interesting Cases

Biased sampling may arise when we concentrate our attention exclusively on the changes that develop in some interesting section of the total group. Consider the case of children who have either unusually tall or unusually short parents. These children, when fully grown, have heights which, on the average, are not as extreme as those of their parents; but it would be fallacious to conclude from this interesting but biased sample that the height of individuals is converging towards some modal value. Adults of the more extreme sizes are derived in part from parents belonging to the middle ranges, and when these parents are fairly represented in the sample it is found that the distribution of the height of adults remains fairly constant from one generation to the next.

The mistake of following the progress of members of the tails of a distribution, and forgetting about the rest, should not be made when the data are available for the complete series. But it sometimes happens in medical research that only the atypical subjects have been given a second examination. This may occur because they excite greater attention than their fellows and appear to repay closer study; they provide welcome relief from the dullness of examining a series composed mainly of normal people.

Some data provided by Toverud (1950) may be used in illustration of this problem. He was interested in the nutrition of pregnant women, and, as part of his investigation, he determined the incidence of anaemia among them. Of 1,077 women examined, 120 had haemoglobin values of less than 12 g. per 100 ml. These 120 women were treated by "regulating the diet and adding iron" and, on subsequent examination, it was found that 82 of the 109 available had haemoglobin values of more than 14.4 g. per 100 ml. This might be taken as evidence that about 11% of the pregnant women required treatment for anaemia and that the treatment used was successful in most of the cases. But the design of the investigation was such that no information could be obtained about those fluctuations in the haemoglobin level which were independent of treatment. Some of the normals, if re-examined, might have been found to have developed temporary anaemia; and some of the anaemic women might have recovered without treatment. These possibilities could have been investigated by making more measurements on the normal group and perhaps by withholding treatment for a time from the supposedly anaemic group—that is, by concentrating less on the interesting cases.

Mass radiography, and other similar preliminary tests, can be regarded as methods of separating off an interesting section of the population for more detailed study. In the initial stages, at least, it is essential that a sample of those who are classified as negative in the screening test should be given the same detailed study as the positive cases receive. Only in this way can it be found whether some subjects have been incorrectly diagnosed as negative. If you direct

attention to the positive group alone, you can never be certain that the screening process is sensitive enough for your needs—that is, you can never find out whether the test fails to detect early cases.

### "Ex Post Facto" Experiments

A great deal of information relevant to problems in medicine has been collected in the form of routine records by agencies such as public health departments. Sometimes these data have been gathered without any special research project in mind, but when they are reconsidered they seem to be pertinent to some problem. These data then constitute what sociologists refer to as an *ex post facto* experiment.

Information obtained in this way is often illuminating, but there are certain limitations to its use, and these are chiefly concerned with the problem of biased sampling. Is it possible to define a universe of which the cases under consideration can be regarded as a sample, and has the sampling been random? If these questions cannot be answered satisfactorily then the standard methods cannot safely be used to test hypotheses concerning the data, and any conclusions drawn may lack objectivity.


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# ADRENAL PSEUDOHERMAPHRODITISM


BY

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Adrenal pseudohermaphroditism, or pre-pubertal virilism, is a syndrome characterized by the masculinization of the female. It is associated with simple enlargement and pigmentation of the adrenal cortex, and the excretion of large amounts of 17-ketosteroid in the urine. The condition is clearly differentiated from true hermaphroditism and the intersexes in two respects. Whereas in both the latter there is a persistence of Wolffian derivatives and no rise in 17-ketosteroid excretion, the reverse is true of adrenal pseudohermaphroditism.

In relation to the aetiology of the disease it is of interest to note that Professor Barr, of London University, Ontario, has examined portions of the skin taken from some of our patients and found in every case the nuclei were of female morphology (personal communications). The available evidence does not advance us beyond the vague generalization that the condition is due to secondary hormonal influences acting upon a genetically determined female embryo during the early stages of foetal development. The critical period of any hormonal action would seem to be between the 11th and 21st weeks—that is, between the time of disappearance of the Wolffian derivatives and the completion of Müllerian development. Whether the stimulus derives from the mother or arises from some factor inherent in the foetal endocrine system are questions which have yet to be determined. Whatever theory is advanced, it must take into account the strong familial element associated with the condition, the evidence for which is cited later.

Our work on this problem of the masculinization of the female began in 1926; since then we have collected 37 cases belonging to the group of congenital pseudohermaphroditism, and the present communication is based on clinical and biochemical data compiled on this series. Previous communications have dealt with a number of the early cases (Broster and Vines, 1933; Broster *et al.*, 1938), but within the past two years many of these, together with more recent patients, have been subjected to a closer and more critical study made possible through the collaboration of Dr. J. Swale, Professor J. Patterson, and Dr. B. Camber.

### General Features

*Symptoms.*—The general features depend on the age of the patient and the severity of the lesion. In infancy the earliest sign is an enlarged clitoris with a persistent urogenital sinus. Later there may be precocious puberty as indicated by premature growth of pubic followed by axillary hair and raised ketosteroid output. As the patients grow up the somatic development is in advance of the chronological age and the short stature is characteristic. If, however, the patient is not seen until the age of normal puberty the diagnosis is made clear when the secondary sex characters of the female do not appear and facial and somatic hair of the male type grows and the voice becomes deep. More recently it has become known that patients suffering from congenital hyperplasia may die in early infancy or childhood from adrenal failure, and in six instances a history was obtained of episodes suggestive of Addisonian crises.

*Hirsuties.*—Except in infants, and one adolescent, hirsuties of male distribution has been a prominent feature in all our cases. In two of the older women temporal recession and apical baldness were present.

*Breasts.*—The great majority of our patients have shown no breast development at puberty. In only eight were they rudimentary, and some of these had received oestrogen therapy.

*Sex Development.*—On examination the clitoris is found to be enlarged and curved downwards. From the area of the fraenum two small folds of skin gradually diverge to encircle a small orifice which is the persistent urogenital sinus. No urethral orifice is visible externally. The cervix and uterus are small and generally not palpable. In only one patient was there a small urethrovaginal fistula. At laparotomy the ovaries have been in their normal position and have not shown any marked macroscopic changes. Some appear normal, while others are fibrotic and cystic. Histologically they show oogenesis and atretic follicles as well as cysts. Three patients about the age of 6 showed numerous ova, atretic follicles, and numbers of cysts typical of isosexual precocity. One of these (M. Ba.), who had normal follicles with some abnormally mature ova, showed a sexuality much in advance of her age. As is reported later, this sexual precocity was related to signs of undue maturity recorded by the electroencephalogram. A few reports recorded luteum cysts, and in one case there was no abnormality apart from suspended activity. Primary amenorrhoea is almost invariably present, although two patients had a slight show after puberty.

### Clinical

*History.*—Significant features in the family histories of 50% (18) of the patients in this series were familial endocrinopathy, maternal disorder during pregnancy, mixed racial origins, or the presence in the individual of associated congenital abnormalities. With adrenal disease in general we have been struck by the frequency with which it occurs

in the offspring of mixed racial marriages, more especially of the Nordic and Mediterranean strains. In this series four families showed affected siblings. Two families were of special interest in that, as well as the affected sister, there was a brother suffering from isosexual precocity due to adrenal cortical hyperplasia. In another family there were two sisters suffering from adrenal pseudohermaphroditism, a brother and sister with congenital dislocation of the hip, and one normal sister. The mother of the fourth family suffered from toxaemia of pregnancy while carrying two pseudohermaphrodite sisters, but not with the other siblings. Endocrine disease, such as diabetes and thyrotoxicosis, was present in four families, and familial hirsuties in another three families. In five instances there was evidence of the "big baby syndrome." The concomitant congenital deformities included "webbed toes," Madelung's deformity, and deformity of the carpus.

*Sexuality.*—Our opinion, arrived at independently of Professor Barr's evidence, that these patients are essentially and fundamentally feminine receives further support from Dr. Randell, who has conducted a psychological investigation into some of these patients and reports: "The fact that these girls suffering from virilism do not show any marked feminine traits accords with the social and psychical concomitants of being 'hairy.' On the other hand, I do not consider that they have marked masculine traits. In every case except one the psyche was orientated in a feminine direction. In adolescent girls this can be said with less assurance as they were immature, but it is certainly true of adults. The level of psychic drive is perhaps generally higher than the average for a woman. The one case excepted, brought up as a boy, still retains masculine traits to some degree. This, however, could be accounted for by the nature of her upbringing." We therefore advise contrary to the expressed views of Wilkins (1950) that irrespective of their background these patients should be brought up as females. To this end we advise removal of the clitoris so as to restore the external genitals to the normal female configuration.

*Encephalography.*—An inquiry into the encephalographic records of these patients has been started by Dr. Frank Elliott, who summarizes his preliminary findings as follows: "Of the five cases tested, four had abnormal records. Two (H. Ba. and M. Am.) showed a degree of maturity quite unusual in children of this age; there were no slow waves, alpha rhythm was well marked, and there was considerable beta activity. These findings are the reverse of what occurs in suprarenal deficiency. C. Ha., on the other hand, exhibited gross bilateral theta activity and some normal theta on overbreathing. These changes were present before cortisone therapy, and are probably due to a lesion in the hypothalamus. Finally, I. Ma., brought up as a boy, had a slightly abnormal record with multiple rhythms in the parietal area. The significance of this observation is not yet clear.

*Somatotypes.*—Most of the patients have been somatotyped by Mr. Wilson, of the photographic department of the Royal Society of Medicine, in order that the details of development and configuration might be studied objectively. The photographs provide not only a permanent record, but also furnish the means of studying the natural history of the disease and the effects of treatment. They clearly demonstrate a characteristic physical type—height generally less than 5 ft. (152 cm.), short muscular body, shoulders broad relative to the hips, legs short relative to the body, deep chest, and tendency to lumbar lordosis with steatopygia.

## Adrenalectomy

Before discussing the operative results in detail, two general observations with regard to adrenalectomy may be recorded. The first point is that, in our experience, the high renal approach via the last rib is the most satisfactory. Secondly, the operation has entered upon a safer phase since the advent of cortisone. The changed situation with regard to adrenalectomy is analogous to that undergone by subtotal thyroidectomy as a result of the introduction of anti-thyroxine compounds. Indeed, the analogy may be pushed further from the technical point of view in that an adrenal is more oedematous, adherent, and difficult to remove after cortisone, as is the thyroid after thiouracil.

Unilateral adrenalectomy (following an exploratory laparotomy) for adrenal pseudohermaphroditism was started in 1926 (Broster *et al.*, 1932) and our early experience was confined to adults. The results were encouraging enough to warrant further trial, and still better results were obtained when we began to operate before puberty. More recently we have carried out subtotal adrenalectomy. In that the results of this treatment are more favourable, we now consider it to be the operation of choice in advanced cases. Out of 37 cases operated on there have been 6 deaths, all of which occurred before cortisone was available. Apart from crises during the immediate post-operative period, only one of our patients has shown evidence of late Addisonian crisis. This exceptional case was treated with cortisone for one year before unilateral adrenalectomy.

Hirsuties when due to adenoma or carcinoma (except with secondary deposits) is shed rapidly after operation and does not recur, but in adrenal pseudohermaphroditism the results are less satisfactory unless bilateral subtotal adrenalectomy is carried out before puberty. The hair on the head does not grow beyond the shoulders, but does so more luxuriantly after operation and to a less extent after cortisone.

It was only when we came to deal with patients who had not yet reached puberty that clinical improvement of an entirely different order was achieved. Six of these cases have now had operative treatment, and since they were of different degrees of severity they received varying forms of treatment—unilateral in one case, subtotal in two cases, unilateral and cortisone in three others. The results of treatment are summarized in Table I.

The secondary sex characters showed a degree of development which was absent in our adult patients. By the application of one of these three methods, the choice being governed largely by the severity of the condition, these young girls may, even if somewhat retarded, now expect to develop their secondary sex characters.

TABLE I

| Patient | Born | Adrenalectomy | Periods | Breasts | Voice | Notes |
|---|---|---|---|---|---|---|
| C. Ha. .. .. | 1939 | Unilateral, 21/11/44 | Regular since 1952 | Normal development | Female | Mild case |
| M. Am. .. .. | 1938 | Subtotal, 11/12/44 and 20/2/48 | 23/5/53, irregular | Normal for age | Deep | Marked case |
| K. He. .. .. | 1938 | Subtotal, 21/2/47 and 10/1/48 | Periods irregular, 25/2/53 | Normal development | Broken; not female | Brought up as a boy. Marked case. Cortisone 17/8/53 |
| I. Ma. .. .. | 1937 | Unilateral, 1949 | One period, July, 1953 | Breasts forming | Higher in tone; pitch feminine | Marked case. Cortisone 6/5/53 |
| H. Ba. .. .. | 1939 | Unilateral, 14/5/48 | None | Retarded | No change | Given cortisone 1/5/53 |
| B. St. .. .. | 1941 | Unilateral, 24/7/53 | One period with cortisone | Well formed | Voice improved | Operation after one year's treatment with cortisone |

## Results

In adrenal pseudohermaphroditism the 17-ketosteroid excretion is essential to diagnosis. The values are always very much raised. In Table II our results are recorded in com-

TABLE II

| Age Range | Normal Range of 17-Ketosteroid Output (mg./day) | Adrenal Cases; Range of 17-Ketosteroid Output (mg./day) |
|---|---|---|
| 2– 5 years .. .. | *0·29–1·20 | 9·8 (1 case) |
| 6– 8 „ .. .. | *0·26–1·55 | 6·5–44·0 |
| 9–12 „ .. .. | *0·23–2·30 | 21·0–56·0 |
| Adult (female) .. | †3·0–16·0 | 38·0–130·0 |

* Values recorded by Wood and Gray (1949). † Values from our own records.

parison with the normals of the corresponding age group. They show, when taken in conjunction with the more comprehensive data for pre-pubertal virilism compiled from the literature by Mason and Engstrom (1950), that the natural history of the disease is associated with steadily mounting 17-ketosteroid excretion, the rise being prolonged well into the third decade. This feature has not always received sufficient recognition, especially by those who have argued that because a post-operative rise in 17-ketosteroid output occurs in some cases it should be taken as an indication that no lasting beneficial effect from unilateral adrenalectomy can be expected. Figs. 1 and 2 (F. Mu. and P. Wa.) illustrate cases in which the operation has resulted in maintaining a relatively low 17-ketosteroid output over a lengthy period, though the more prolonged investigation of Case P. Wa. has revealed a late rise. The patient whose excretion is recorded in Fig. 3 (P. Go.) was subjected to a double operation (right adrenalectomy followed by left hemi-adrenalectomy), and has maintained an almost normal 17-ketosteroid output during the whole of the perod she was investigated.

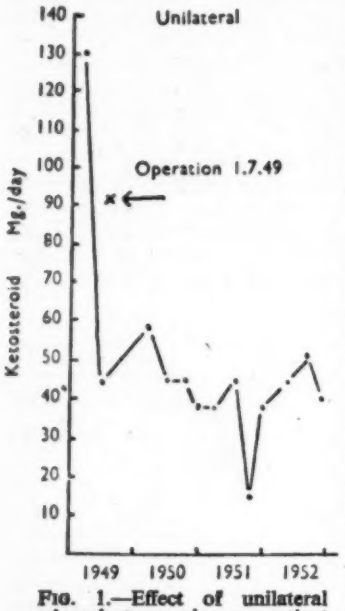


FIG. 1.—Effect of unilateral adrenalectomy in a patient (F. Mu.) aged 35–38.

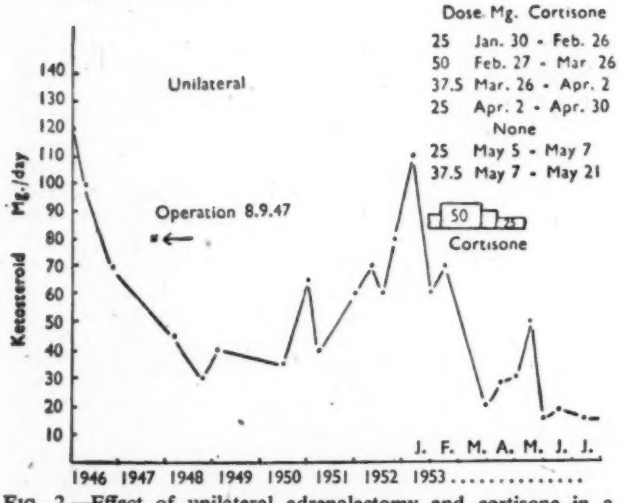


FIG. 2.—Effect of unilateral adrenalectomy and cortisone in a patient (P. Wa.) aged 15–22.

Our experience shows that when unilateral adrenalectomy is performed on adolescents and adults there is some degree of clinical improvement in nearly all cases. The patients look less coarse and more refined, the subcutaneous fat is softer and more evenly distributed, the texture of the skin and the complexion are improved, acne lessens, the hair of the head grows longer and loses its greasy appearance, while that on the body becomes more amenable to depilation. In these cases, however, there is no very obvious correlation between the degree of clinical improvement and the extent of the depression of the 17-ketosteroids after operation.

### Dehydroepiandrosterone (D.H.A.) Excretion

Of the 17-ketosteroids excreted in the urine, D.H.A. is of special interest because it is believed to be derived solely from the adrenal cortex. When it was found in virilizing adrenal tumours that D.H.A. amounted to over 50% of total 17-ketosteroids it became important to find a ready, direct test showing its preponderance in the urine. A test fulfilling this purpose was devised by Patterson (1947). It is based on the finding that when D.H.A. is subjected to the action of sulphuric acid under certain conditions a blue colour results. As only virilizing tumours yield enough D.H.A. in the urine to give a positive result under the prescribed technique, the test could be used for diagnosing the presence of this lesion. The work has now been extended so as to provide a quantitative method for measuring D.H.A. excretion in patients suffering from adrenal pseudohermaphroditism (Patterson and Swale, 1953).

The application of this method to the present series shows that, biochemically, the patients fall into two distinct groups. The first (type $\alpha$) is characterized by a relative absence of D.H.A., whereas the second (type $\beta$) shows appreciable amounts of D.H.A., the most important of the beta 17-ketosteroids. Of the 19 investigated, 6 were of type $\alpha$ (excreting less than 0.5 mg. of D.H.A. a day) and 13 were of type $\beta$ (excreting 1–25 mg. a day). The detailed results for type $\beta$ cases are recorded in Table III.

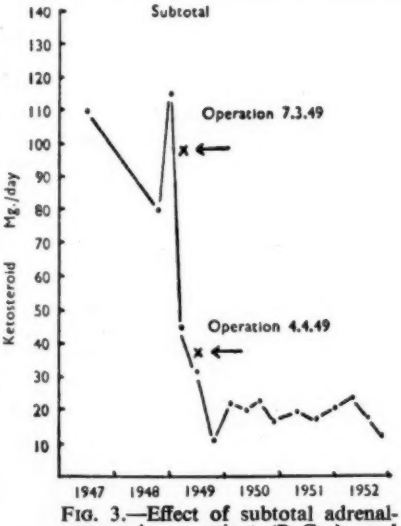


FIG. 3.—Effect of subtotal adrenalectomy in a patient (P. Go.) aged 22–27.

In relation to these findings it may be pointed out that Scowen and Harris (1951) failed to find D.H.A. in appreciable quantity in the urine in a study of nine cases of adrenal pseudohermaphroditism, whereas Dingemanse *et al.* (1946), provided evidence for the presence of large amounts in their series. These apparently conflicting results are reconciled by the demonstration here of the existence of two types within the same clinical group.

The possible clinical significance of the two different biochemical types is now under investigation. The amount of D.H.A. excretion does not appear to bear any obvious relation to the clinical picture, and in the light of our present observations it cannot be said that D.H.A. excretion is a

TABLE III.—*D.H.A. Excretion in Cases of Type β*

| Patient | Age | Total 17-K.S. (mg./day) | D.H.A. (mg./day) | D.H.A. as percentage of Total 17-K.S. | Remarks |
|---|---|---|---|---|---|
| C. St. | 31 | 88·0 | 18·0 | 20·0 | Pre-operative |
| J. Cl. | 17 | 78·0 | 5·4 | 7·0 | ,, |
| B. St. | 12 | 52·6 | 6·8 | 13·0 | ,, |
| A. He. | 22 | 69·0 | 19·0 | 27·5 | ,, |
| J. Ki. | 32 | 74·0 | 6·4 | 8·7 | Unilateral adrenalectomy, 1936 |
| A. Go. | 32 | 45·0 | 9·1 | 20·2 | Unilateral adrenalectomy, 1937 |
| R. Mo. | 18 | 80·0 | 25·1 | 31·3 | Unilateral adrenalectomy, 1946 |
| J. Pa. | 17 | 84·0 | 6·2 | 7·5 | Unilateral adrenalectomy, 1946 |
| P. Wa. | 22 | 84·0 | 14·9 | 17·7 | Unilateral adrenalectomy, 1947 |
| F. Mu. | 38 | 38·8 | 2·5 | 6·4 | Unilateral adrenalectomy, 1949 |
| J. Du. | 12 | 38·5 | 1·5 | 3·8 | Unilateral adrenalectomy, 1950 |
| M. Am. | 14 | 43·0 | 3·4 | 8·0 | L. adrenalectomy, 1944. R. hemi-adrenalectomy, 1948 |
| P. Go. | 27 | 28·5 | 1·1 | 3·9 | R. adrenalectomy, 1949. L. hemi-adrenalectomy, 1949 |

better index of the adrenocortical function than is the total 17-ketosteroid output.

Comparison of the effect of operation and of cortisone on D.H.A output in cases conforming to type $\beta$ has not proceeded far enough to admit of definite conclusions, but preliminary work indicates that as a result of unilateral adrenalectomy D.H.A. is reduced in much the same proportion as the total 17-ketosteroids. In other words, there is no deviation from type $\beta$. The effect of treatment with cortisone compared with that of unilateral adrenalectomy depends on the dosage. When only enough cortisone has been administered to halve the total 17-ketosteroid output—that is, corresponding approximately to the reduction that can be achieved by the removal of one adrenal—there is again no deviation from type $\beta$. If, however, enough cortisone is given to bring down the total 17-ketosteroids to normal values, the D.H.A. is almost completely eliminated, signifying a change from type $\beta$ to type $\alpha$.

**Summary**

A short clinical and biochemical review of 37 cases of adrenal pseudohermaphroditism is presented.

Further biochemical studies show, on the basis of dehydroisoandrosterone excretion, that these patients fall into two distinct groups.

The effects of unilateral and bilateral adrenalectomy on 17-ketosteroid excretion are shown.

Observations of the action of cortisone on 17-ketosteroid excretion are also discussed.

Treatment is more effective when undertaken before puberty.

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# PORPHYRIA

BY

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Porphyria is a disorder involving the pyrrole pigments which take part in respiratory metabolism. It is a familial condition characterized by chronic mild neurological and cutaneous symptoms with occasional acute exacerbations. I have personally attended 12 cases of acute porphyria. The first three of these patients died, the last nine recovered. They were from eleven different family groups.

In each family the genealogical tree has been worked out in the fullest detail possible. Some of the groups were large—for instance, in the first family there are 460 descendants of the first member of the family who is known to have had the typical sensitive skin. As will be seen, many in each family group have inherited porphyria. The sex distribution was about equal, but the most severe cases of acute porphyria were in women between the ages of 19 and 50. The reason for this predominance of women is discussed below. All the families seen were Afrikaners perhaps related far back in South African history. It is a common condition in South Africa, and Barnes (1945, 1951) has already published the history and laboratory findings of over 40 cases. The mild cutaneous type is common in the Bantu. The condition has also been described in cattle (Fourie, 1936).

The porphyrin structure is present in haemoglobin and in certain other respiratory enzymes. When porphyrins are produced in excess they are excreted in the urine as uroporphyrins, as coproporphyrins, or as a colourless chromogen, porphobilinogen. They are also excreted in the faeces. Porphyrins may colour the urine red or reddish brown. Garrod (1923) considered that porphyria belonged to the group of familial disorders which were inherited as "inborn errors of metabolism." The disturbance in metabolism is aggravated particularly by certain drugs and by pregnancy. Porphyrinuria, usually an excess of coproporphyrins, may also occur in liver disease, anaemia, or after poisoning by certain chemicals, in individuals who do not suffer from familial porphyria.

My experience is limited to porphyria in the adult, when it presents a familial syndrome which is characteristic. Unfortunately, however, the syndrome can best be seen in retrospect, and during a remission it is often difficult to diagnose. In the acute stage diagnosis may be made too late to save the patient's life. It is a syndrome that is not well described in the medical textbooks, and if it is to be diagnosed early a much clearer concept of the condition will have to become widespread knowledge among the profession. However, it is extremely important that the diagnosis be made, because frequently it is the doctor who is unwittingly responsible for the patient's death.

## The Syndrome

Porphyrics often have an apparently neurotic make-up. Many have complained for years about various pains, particularly in the abdomen. Because of these pains they often become drug addicts, taking barbiturates, aspirin, or a variety of patent medicines. They have usually seen many doctors, and unfortunately they may have had a number of abdominal operations. The urine is generally normal in colour, but, on questioning, patients may recall that their urine has been red during an illness in the past. The abdominal pain sometimes occurs in acute attacks accompanied by vomiting, when a diagnosis of appendicitis, intestinal obstruction, or some other abdominal emergency may be made. Patients, or some of the relatives, frequently have a skin that breaks down easily, forming blisters and then ulcers. This sensitivity of the skin is not usually apparent until adult life. The exposed areas of skin are particularly affected—the back of the hands and, in women, the front of the legs. Sunlight and minor injury appear to be precipitating causes. This ulceration is more common during pregnancy. The ulcers are usually small and multiple, and take a long time to heal. They are deep enough to leave permanent scars. Rather surprisingly, the ulcers of the skin are often most troublesome when the condition is quiescent, and may be absent during an acute attack. Conjunctivitis is a not uncommon symptom, and small pigmented spots that fluoresce in ultra-violet light may be seen in the retina.

During pregnancy the patient is usually much worse, perhaps partly because she is then given sedatives. There is often a history that previous pregnancies were terminated because of pains, vomiting, and hysteria.

In many cases a family group is first found to be porphyric when one of its members has an acute attack. More likely than not this acute attack follows an abdominal operation, particularly if thiopentone has been given as an anaesthetic, or it occurs during pregnancy. Women are more prone to be operated upon for lower abdominal pain than men; this fact and pregnancy probably account for

the frequency of acute attacks in women. In my experience the chronic stage is found just as commonly in men. After operation the patients' behaviour is usually hysterical. They complain of severe pains all over the body, but particularly in the abdomen. Their operation wound is slow to heal; they are uncooperative, and it is difficult to maintain their nutrition. After a few days they complain of weakness, which at first may be regarded as hysterical. Then it is realized that they have developed a lower motor neurone type of paralysis. Their reflexes disappear, their pupils are dilated, and their heart rate is rapid. The blood pressure may be raised. During the acute illness they pass reddish-brown urine which darkens on standing. As the paralysis progresses their mental symptoms and abdominal pains lessen, and they often have an awareness of approaching death. At this stage the prognosis should be guarded, but it is not as grave as was formerly thought. If the patient does not die, the peripheral neuritis may persist for many months.

Evidence of impaired liver function can be found during an acute attack. For instance, the icteric index is raised and the albumin/globulin ratio is altered. The blood chloride may be lowered if there has been much vomiting.

There is usually a leucocytosis. The cerebrospinal fluid is normal. In my experience the electrocardiogram shows a tachycardia, but no very characteristic change. Chemical and spectroscopic examination of the urine confirms the presence of porphyrins.

Post-mortem examination of the liver shows hepatitis and a deposit of pigment in the liver cells. There is strong evidence that in the adult the production of porphyrins takes place in the liver. Examination of the spinal cord shows degenerative changes in the anterior and posterior horn cells; the sympathetic ganglia show similar changes. There is a demyelinization of peripheral nerves (Goldman and Kaplan, 1951).

### Differential Diagnosis

The chronic or mild case seen in the consulting-room, with complaints of abdominal and other pains for which no organic cause can be found, presents a difficult diagnostic problem. Diagnosis depends on a very full personal and family history, with special reference to "nervous breakdowns," abdominal pains, operations, health during pregnancy, drug-taking, and any personal or familial tendency for the skin to blister. Inquiry should be made into the cause of death of any blood relation, death from generalized paralysis being of particular significance. Often an older member of the family, perhaps an aunt, can cast great light on the problem by describing the skin lesions or death from paralysis of members of a previous generation. Other organic disease must of course be excluded. A history in any member of the family of passing red urine may be a most useful clue. The urine should be tested chemically and spectroscopically, as a positive result will confirm the diagnosis. Sooner or later porphyrins will usually be found in the urine on careful spectroscopic examination.

When the patient is first seen during an acute attack the differential diagnosis must be made from hysteria, appendicitis, or intestinal obstruction. The attack generally follows drug-taking or an anaesthetic, but it may arise apparently spontaneously, particularly during pregnancy. If paralysis has already developed, it must be differentiated from poliomyelitis, the Guillain-Barré syndrome, or hysteria. The history and examination of the cerebrospinal fluid and of the urine will settle the diagnosis. At this stage porphyrins are present in excess in the urine. An increased excretion of porphyrins may also occur in hepatitis in an individual who is not suffering from familial porphyria, but the amount is less and porphobilinogen is not usually present.

### Tests for Porphyrins

In the acute stage the urine may immediately suggest porphyria because of its red colour, or it may darken on standing in sunlight, particularly after the addition of hydrochloric acid. If the urine is normal in colour Ehrlich's aldehyde saturated with sodium acetate should be added, the urine shaken, and chloroform added. When porphobilinogen is present a red colour will appear in the aqueous solution (the Watson–Schwartz test). Porphyric urine will fluoresce on exposure to ultra-violet light. The presence of porphyrins can be confirmed by spectroscopic examination using a thick layer of urine and a good spectroscope; the porphyrin absorption bands will then be seen. The methyl esters of porphyrins have a characteristic melting-point after crystallization from urine. It should be remembered that blood, beetroot, or drugs may also cause red urine.

In the chronic or latent stage the usual tests for porphyrins may be negative. Both the urine and the faeces should be examined by a biochemist who has had considerable experience in testing for porphyrins. If the urine has to be sent away, a few drops of chloroform may be added as a preservative. A 5-in. (12.5-cm.) layer of urine should be examined spectroscopically after the urine has first been filtered carefully. This is usually a more sensitive test than looking for fluorescence in ultra-violet light. However, excess porphyrin may not be present during a remission. As an experiment 15 specimens of urine from proved porphyrics, in the chronic or latent stage, were sent to a biochemist especially interested in porphyria detection. Porphyrins were found in excess in four specimens. Another specimen of urine was sent from most of the same patients, and three of the previous four were still positive but one was now negative. Three more specimens, however, were now positive. A positive result was finally obtained in 12 out of the 15 cases. These specimens of urine were sent in identical numbered bottles with 18 controls. All the controls were negative.

### Case Histories

Only a brief summary will be given of seven cases of acute porphyria. They all come from different family groups, and in each case a genealogical tree has been worked out in the greatest detail possible. All known members of the family groups were contacted. Members of the family have been regarded as porphyrics only if the spectroscopic examination of the urine was positive, or if they showed the typical skin lesions and their immediate relatives were proved porphyrics. In the families studied porphyria was inherited as a Mendelian dominant. Detailed family trees and the inheritance of porphyria will be discussed in a subsequent article.

*Case 1.*—February, 1951. A nurse aged 19 suffered severe abdominal pains after the use of barbiturates. As she was thought to have an intestinal obstruction a laparotomy was carried out and thiopentone was used to induce anaesthesia. After the operation she was delirious, the abdominal pains increased, and she vomited repeatedly. Within three days she was completely paralysed, her pulse was rapid, and her pupils were dilated and fixed. Her urine was red and was strongly positive for porphyrins. She was fed intravenously, but died eight days after the operation.

Over the course of a year a very detailed genealogical tree was obtained. All living members of the family were contacted. The original head of the family, who is still remembered by one remaining son-in-law, died in 1884. He himself had a sensitive skin that had blistered repeatedly and left numerous scars on his hands. As descendants he had 10 children, 61 grandchildren, 173 in the third generation, 197 in the fourth generation, and already 19 in the fifth generation. Fifty-one inherited a sensitive skin that blisters and ulcerates easily. A further 6 women have porphyrinuria, but no history of a sensitive skin. At least 57 of the family appear to have inherited porphyria (22 male, 35 female). Thirty-nine of these are still alive, and excess porphyrins have been found in the urine of 37 of them. Of the remainder eight women and one man have died with typical symptoms of acute porphyria, including two of the sisters of Case 1. Altogether 402 members of

this family have now had their urine tested for porphyrins; all the others were negative.

*Case 2.*—February, 1951. A married woman aged 42 had been regarded as neurotic all her life. In 1932, following thiopentone anaesthesia, she became paralysed and was unable to walk for six months. She was seen by me after a hysterectomy, during which she was given thiopentone; she complained of severe abdominal pains and vomited repeatedly, and became paralysed over the course of three weeks. Porphyrins were found in her urine. She died six weeks after the anaesthetic. Of the 162 adult relations traced on the affected side of the family, 39 (17 male, 22 female) had inherited porphyria; most of these had a sensitive skin that blistered easily. Her brother and two other members of the group died with symptoms of acute porphyria.

*Case 3.*—July, 1952. A married woman aged 41. The skin of her hands and the front of her legs had blistered easily all her life. Following thiopentone anaesthesia for operation on varicose veins she developed abdominal pains and vomiting, and became paralysed. Porphyrins were found in the urine, which was reddish black. She died ten days after the operation in spite of A.C.T.H. and intravenous drips. Of 44 adult relatives on the affected side of the family 17 (7 male, 10 female) were porphyrics. A male cousin of this patient also had an attack of acute porphyria after taking barbiturates. He did not become paralysed and made a good recovery.

*Case 4.*—August, 1952. A married woman aged 27 had recurrent attacks of vomiting and abdominal pain during her pregnancies. She became partially paralysed after thiopentone anaesthesia when the third pregnancy was terminated, but she recovered. Six months later the abdominal pains recurred after the use of barbiturate sedatives. She was given thiopentone for a laparotomy. A few days afterwards she became delirious and partially paralysed. Porphyrins were present in her urine. She slowly recovered, but is now troubled with recurrent blisters and ulcers on her hands and arms. Of 114 adult members of her family on the affected side 24 (17 male and 7 female) have inherited porphyria. Five (3 male, 2 female) other members of the family have died from generalized paralysis after drugs and anaesthetics.

*Case 5.*—March, 1953. A married woman aged 35 had had repeated operations for abdominal pains. She had severe attacks of vomiting and pain during her pregnancies. After thiopentone anaesthesia for a hysterectomy she became delirious. Her urine gave positive porphyrin reactions. Her liver function was impaired. Although all drugs were stopped she became completely paralysed within 48 hours. She was given A.C.T.H. and fed by intravenous drip. She is slowly recovering, and five months later was starting to walk. Of 25 adult members of the family on the affected side 17 have inherited porphyria.

*Case 6.*—March, 1953. A married woman aged 36 had suffered from recurrent blisters on the back of her hands and on the front of her legs since she was 18. Her first pregnancy was terminated because of vomiting and the passing of red urine. Following thiopentone anaesthesia for appendicectomy she was hysterical, complained of severe abdominal pain, and vomited repeatedly. Her urine became dark and porphyrins were present. Although all drugs were stopped and she was fed intravenously, she became almost totally paralysed. During the next six months she made a good recovery, but her jerk responses are still absent and there is impaired liver function. Nine of the 43 adult members of the family on the affected side have inherited porphyria.

*Case 7.*—December, 1948. A married woman aged 29 vomited repeatedly during her second pregnancy and complained of severe abdominal pain. She became jaundiced and her urine was reddish brown. She was given thiopentone for a curettage. After the operation she was delirious, and within three days she was totally paralysed. She recovered, but was in hospital seven months. She lost a great deal of weight during this illness. Two years later she was given thiopentone for dental extractions; she again became delirious, her urine was reddish brown, and all the tests for porphyrins were positive. Again she became paralysed, but recovered in about five months. Her skin now blisters on the back of the hands and at the ankles. Seven of the 45 adult members of the family on the affected side have inherited porphyria.

*Other Cases.*—Five men have also been seen by me during attacks of acute porphyria; one has already been mentioned. Of the other four, one became partly paralysed after thiopentone, and one had an acute cutaneous reaction with hepatitis after painting wood with a preservative, pentachlorophenol. The remaining two became acutely ill with severe abdominal pains and vomiting, with a strongly positive red urine, after taking phenobarbitone. They recovered without becoming paralysed. Two other cases of porphyria (one man and one woman), belonging to other groups, were diagnosed in the consulting-rooms during the latent phase. They were complaining of abdominal pains and had been regarded as neurotic. Porphyrins were found in their urine. Several of their relatives were also affected. From these 13 family groups 216 porphyrics have been traced and warned.

### Treatment

When porphyria is diagnosed in the chronic stage treatment consists primarily in stopping all drugs that may be aggravating the condition. This includes a wide range of substances, particularly sedatives such as barbiturates. The doctor must advise the patient that he may suffer some pain, but that all will be well so long as certain drugs, including patent medicines and alcohol, are scrupulously avoided. Penicillin may safely be given, but sulphonamides are harmful. Aureomycin should not be given intravenously because of its possible deleterious effect on the liver. The extreme danger of thiopentone anaesthesia must be pointed out to the patient and to the relatives, and to convince them they should be given a few anonymous case histories to read. If an operation is absolutely unavoidable because of serious organic disease ether is probably the least harmful anaesthetic. Many porphyric patients seen by me have had anaesthetics other than barbiturates and made good recoveries. If the skin is photosensitive the patient should keep out of the sun as much as possible, and wear a hat and gloves out of doors. Protective creams, such as 5% tannic acid in vanishing cream, are of some value.

In the acute stage good nursing, preferably in a private room in a hospital, is probably the most important single factor in aiding recovery. As there is as yet no specific antidote for porphyria, treatment depends on maintaining the patient's general condition and avoiding any harmful drug. These patients must not be given sedatives, except perhaps a little paraldehyde. In my experience it is possible to keep them fairly comfortable with the aid of placebos such as vitamin tablets. If there is vomiting the nutrition and electrolyte balance must be carefully watched and maintained by intravenous feeding. Repeated examination of the blood and urine chlorides and the blood potassium may be required. As there is often evidence of liver damage I give these patients a high-protein high-carbohydrate diet and a high fluid intake. I also give them methionine, vitamin $B_{12}$, vitamin B complex, and vitamin C. Dimercaprol protects the nerves against certain nerve poisons. It was given to one patient who was threatened with paralysis of respiration, but nevertheless she died: there is no evidence that it helps in porphyria. A.C.T.H. was given to seven patients; it certainly made them feel better and appeared to be of value. As a last resort an artificial lung can be used, but if respiration is paralysed the patient usually dies. In the recovery stage physiotherapy is of the greatest importance. Recovery from paralysis takes many months if the paralysis is severe.

Once a case of porphyria has been diagnosed it is the doctor's responsibility to investigate the family history fully. The best method is to work out a complete family tree,

and this may take several months. Inquiry must then be made in order to discover which side of the family is affected and which members on the affected side have inherited porphyria. The urine of the relatives should be examined spectroscopically for porphyrins. It must not be forgotten that the syndrome will present in different ways in different members of the group. Many will have complained of symptoms the cause of which will not have been known. The doctor will be greatly rewarded when he makes the correct diagnosis in a patient who has long been regarded as neurotic, and who has had perhaps a number of operations on account of abdominal pains. All affected members of the group must be interviewed. Porphyrics should be given a letter stating the evidence on which the diagnosis has been made, and mentioning the danger of barbiturates and other drugs in this condition. They should show this letter to any doctor they may consult in the future.

**Summary**

Porphyria, a serious familial disorder, is common in South Africa.

In the chronic or latent stage the diagnosis will be made only if the doctor is alive to the possibility that the disorder may cause symptoms which are apparently neurotic, particularly abdominal pains.

In the latent stage no reliance can be placed on a negative urine test, as at this stage excess porphyrins may not be excreted. Diagnosis depends on a full personal and family history. During an acute attack examination of the urine will confirm the presence of porphyrins.

In acute attacks of obscure abdominal pain the abdomen should be opened only if there are definite indications that surgery is necessary, and after the urine has been carefully examined for porphyrins.

The increased use of barbiturates in the routine treatment of nervous disorders may well be responsible for bringing this syndrome to the fore. Intravenous barbiturate anaesthetics are particularly likely to precipitate a severe attack, often with resultant paralysis.

If one case of porphyria is diagnosed it is the doctor's responsibility to go very fully into the family history and interview as many relations as possible. This will lead to the discovery of other undiagnosed cases and result in preventing much suffering and unnecessary operations.

In the relatives of the cases described here, different manifestations of the syndrome were seen in different members of the family group. This suggests the unitary nature of porphyria in the adult, and that division into subtypes is artificial.

I would like to thank the doctors who called me in consultation to see these patients for their permission to publish the case histories, and for their unfailing help and encouragement in the preparation of this article. Also Mr. Barnes, of the South African Institute for Medical Research, Johannesburg, for investigating many specimens of urine for me. My thanks are also due to Dr. Harington and the staff of the Research Institute, Port Elizabeth.

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# INTRA-ARTERIAL TRANSFUSION

BY

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Intra-arterial transfusion is considered to be of great value in the treatment of haemorrhage. We agree that this is the main indication for its use, but the object of this paper is to report our observations on the value of the method in combating circulatory collapse due mainly to causes other than bleeding. An excellent survey, historical, experimental, and clinical, of the literature concerning the use of the intra-arterial route for transfusion has been published by Seeley and Nelson (1952). Valuable experimental and clinical evidence is given by Porter *et al.* (1948), Robertson *et al.* (1948), Jones *et al.* (1950), and Bingham (1952), among many others.

In general, where the effect of peripheral anoxia has been sufficient to cause relaxation of peripheral vessels and an increase in the volume of the vascular bed, with stagnation of the blood flow, fluids given intravenously will tend to accumulate in the relaxed venous channels. Vasopressors are often ineffective in restoring tone to the anoxic vessels, prolonged hypotension may have led to myocardial damage, and venous congestion may be present. Intra-arterial transfusion may even then restore the blood flow enough to reverse stagnation and permit adequate tissue oxygenation once more. When bleeding is not the cause of the collapse, such an improvement is only a respite during which definitive treatment may be applied, but it is an essential respite.

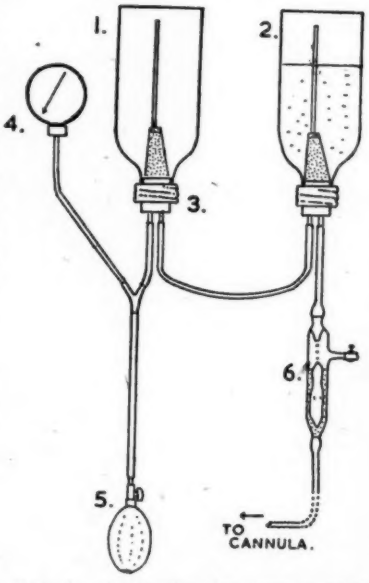


FIG. 1.—Apparatus for intra-arterial transfusion. 1=Air reservoir. 2=Blood. 3=Safety screw caps. 4=Aneroid manometer. 5=Sphygmomanometer bulb. 6=Drip chamber with float (Macintosh and Pask, 1941).

**Apparatus**

In brief, the method of intra-arterial infusion consists in the introduction of whole blood or blood substitutes under pressure into a suitable artery. The apparatus* may be a simple transfusion set with a double bellows as the source of pressure, or take a more complicated form incorporating a manometer for measuring the infusion pressure. An oxygen tank with control valve is used as the motive force in some apparatus. If vasospasm is pronounced, a syringe and three-way stopcock are use-

*Since this paper was written we have used a form of rotary roller pump for rapid transfusions, and have found it superior to the apparatus described, and less apt to provoke vasospasm.

ful; the intermittent pressure of this method may provoke less reflex spasm of the vessel in response to the reversed circulation. This method is less prone to the danger of air embolism, a disaster which, when using a pressure drip, is prevented only by constant vigilance on the part of the administrator and by the use of a safety drip chamber with a float which beds down and produces an air-tight seal should the chamber become empty (Macintosh and Pask, 1941).

We have modified the apparatus described by Seeley (1951) to include such a drip chamber (Fig. 1). The set, less the pressure bulb and manometer, is autoclaved and kept in a sterile drum. For use, a saline bottle is emptied and attached as the air reservoir, the blood bottle being fixed to the other cork. Screw caps fitting the standard M.R.C. bottles are incorporated in the apparatus to prevent ejection of the corks by positive pressure.

### Choice of Artery

The artery used for transfusion has varied with different authors; the radial, femoral, dorsalis pedis, or posterior tibial arteries, and the abdominal aorta have all been used. In the case of arterial bleeding, the site of transfusion should obviously not be distal to the point of haemorrhage. We prefer the left radial artery for the following reasons. The limb is almost always readily accessible, and good arterial anastomosis is available in the hand and arm to provide alternative channels should the vessel be sacrificed. It is easy to perform a sympathetic block to relieve vasospasm in this region, and the anatomical landmarks make identification of the radial artery at the wrist a simple matter.

In extreme shock, with the pulse impalpable and the vasospasm marked, percutaneous arterial puncture is likely to be almost impossible, and there is aways a risk of haemorrhage after the withdrawal of the needle. Consequently, we prefer open exposure of the radial artery and ligation at the end of the transfusion, believing that there is no objection to such a course in this situation, and, further, that even if arterial suture were performed subsequent thrombosis would commonly occur.

### Technique of Intra-arterial Transfusion

A preliminary brachial plexus or stellate ganglion block with 20 ml. of 1% lignocaine hydrochloride is performed if the urgency of the case permits. The skin of the left wrist is cleaned with ether and the area towelled up. Then 2 ml. of 2% procaine is infiltrated over the site of the radial artery, an incision is made—longitudinal if the vessel is palpable, transverse if not—and the artery exposed. A swab soaked in 2% procaine is laid over it while the apparatus is set up. Next, two ligatures are passed around the vessel and the distal one is tied. A V-shaped nick is made in the vessel and the cannula inserted, directed towards the heart. The proximal ligature is then tied to secure the cannula and 2 ml. of 2% procaine is injected into the artery via the drip tubing and the infusion begun. The rate and pressure at which transfusion is conducted will vary from patient to patient, and will depend upon the arterial blood pressure and the degree of arterial spasm. If the blood pressure is low and spasm is not pronounced, the drip will run fast at first, gradually slowing as the arterial blood pressure returns to normal levels. An initial pressure gradient of 50 mm. Hg has been suggested as suitable. The volume of fluid needed will vary with the condition causing hypotension, but a satisfactory response and clinical improvement usually occur rapidly after as little as 250 ml. has been given; the final total has often been between 1 and 2 litres.

At the end of the transfusion a further 2 ml. of 2% procaine is injected, the cannula withdrawn, and the vessel ligated. The limb is kept cool if there is any evidence of defective circulation, and, in this case, further improvement may be gained by a 0.2% procaine drip intravenously and by repetition of the brachial plexus block.

We have not yet tried the local application of warm papaverine 1:80 or 1:40 solution as recommended by Kinmonth (1952). This may be more effective than procaine in relieving local vasospasm.

From a practical aspect there are, we think, two chief points to be considered: (1) has the method any great advantage to offer over the intravenous route; and (2) when should its use be considered? These problems are related, for in conditions of profound shock, in which theoretically intra-arterial infusion is of the most value, it may be extremely difficult to get an intravenous drip to run at all, and, indeed, the failure of intravenous therapy to produce benefit may well indicate the use of the arterial route. A third problem is the possibility of ischaemia due to damage to the artery used for transfusion. In the case of the radial artery it seems that if the patient makes a recovery from his hypotension and circulatory collapse, there is little to fear on this score.

TABLE I.—*Summary of 17 Reports on the Use of Intra-arterial Transfusion*

| Author | No. of Cases | Reason for Transfusion | Survival | Initial B.P. | Route | Ischaemic Sequelae |
|---|---|---|---|---|---|---|
| Porter *et al.* (1948) | 12 | Haemorrhage, 8<br>Coarctation of aorta, 4 | 5<br>4 | 0 | Radial | 1, Gangrene<br>2, Blistering of skin<br>2, Discoloration of skin |
| Robertson *et al.* (1948) | 12 | Haemorrhage, 10<br>Others, 2 | 8<br>0 | Mostly 0 | „<br>Post. tibial | — |
| Ciliberti and Dickler (1950) | 1 | Haemorrhage pulm. artery | 1 | 0 | Radial | Nil |
| Kay and Hacker (1947) | 1 | Haemorrhage int. mammary | 1 | 0 | Aorta | „ |
| Haxton (1952) | 10 | Various, mainly haemorrhage | 7 | — | „ | „ |
| Bayles (1951) | 1 | Haemorrhage prostate | 1 | 0 | Radial | „ |
| Gold *et al.* (1949) | 1 | Intestinal obstruction. High spinal | 1 | 0 | „ | „ |
| Jaquenoud (1952) | 3 | Haemorrhage, 2<br>Intestinal fistula, 1 | 0 | — | „ | — |
| Vignon (1952) | 1 | Haemorrhage, post-partum | 1 | 0 | „ | Oedema and paralysis of arm |
| Silber *et al.* (1951) | 9 | Coronary thrombosis | 2 | 0 | „ | — |
| Ziccardi and Madden (1951) | — | " Prophylaxis " | — | — | „ | — |
| Bingham (1952) | 100+ | Shock and " prophylaxis " | — | — | „ | 2 Partial ischaemia of hand |
| French (1951) | 2 | Haemorrhage | 2 | 0 | „ | 1 Contracture of finger |
| Kohlstaedt and Page (1943) | 3 | Injury and haemorrhage | 1 | Below 50 | „ | 2 Slough of skin of forearm |
| Metheny *et al.* (1949) | 1 | Ruptured aneurysm | 0 | 60/50 | Femoral | — |
| Devitt and Wigderow (1951) | 1 | Haemorrhage pelvic | 1 | 0 | Common iliac | Nil |
| Seeley (1951) | 7 | Haemorrhage, 3<br>Others, 4 | 2<br>2 | Vary | Aorta, Radial, Femoral | „ |

Table I presents a summary of cases of intra-arterial transfusion collected from the literature. It will be seen that haemorrhage from various sites has formed the chief indication for therapy sometimes following the failure of intravenous transfusion to correct the hypertension, but often as the first choice. It is in this group, undoubtedly, that the results are best. Ischaemic sequelae were noted in only 10 cases, and were not seen in any of the cases of deliberate controlled hypertension by arterial bleeding and reinfusion, lending support to the view that the sustained return of the blood pressure to normal levels is a major factor in their prevention.

### Discussion of Cases

Two patients were given intra-arterial blood because of haemorrhage (Table II).

*Case 1.*—A man aged 56 was admitted with severe haematemesis from a duodenal ulcer. The response to prolonged intravenous blood therapy was poor. He collapsed and became pulseless and comatose. Intra-arterial transfusion quickly improved his

TABLE II.—*Cases Receiving Intra-arterial Transfusion*

| Case No. | Age | Condition | Initial | | Vol. of Fluid | Time (min.) | Final | | Result |
|---|---|---|---|---|---|---|---|---|---|
| | | | B.P. | Pulse | | | B.P. | Pulse | |
| 1 | 56 | Haematemesis from duodenal ulcer. No response to much blood I.V. Sudden collapse and coma | 60/? | 130 | 4,000 ml. blood | 45 | 135/70 | 160 | Duodenotomy—recovery. Partial gastrectomy for biliary leak three days later. Gradual deterioration. Died 4th post-operative day |
| 2 | 60 | Combined excision of rectum. Perineal haemorrhage | 0/0 | ? | 2,500 ml. blood | 50 | 100/60 | 100 | Operation completed. Recovery |
| 3 | 61 | Mesenteric embolus. Operative shock. Auricular fibrillation. Heart failure | 0/0 | 96 | 650 ml. blood | 20 | 70/50 | 88 | " " " |
| 4 | 68 | Volvulus of small gut. Heart failure. Pulmonary oedema. Peripheral failure | 100/? | — | 1,000 ml. blood | 60 | 120/? | — | Improved. Pulmonary oedema less. No operation. Died 24 hours later |
| 5 | 42 | Late perforated ulcer. Peripheral failure. Dyspnoea. Moribund | 0/0 | 140 | 2,000 ml. blood | 130 | 85/? | 100 | Suture of ulcer—prolonged hypotension. Temporary oliguria. Complete recovery |
| 6 | 51 | Peritonitis. Perforated duodenal ulcer. Peripheral circulatory failure. Moribund | 0/0 | — | 1,000 ml. blood | 20 | 100/80 | — | Suture of ulcer. Died 9 hours post-operatively |
| 7 | 19 | Perforated ulcer. Comatose | 0/0 | 150 | 800 ml. blood | 70 | — | — | Became conscious—sudden dyspnoea. Died during transfusion |
| 8 | 50 | Partial gastrectomy day before. Peripheral circulatory failure. Death imminent | 0/0 | 160 | 2,000 ml. blood and dextran | 55 | 85/? | — | Diagnosis in doubt. No operation. Died 8 hours later. Necropsy: Bleeding and leak from duodenal stump |
| 9 | 50 | Partial gastrectomy. Ileus. Peripheral circulatory failure. Sudden collapse | 20/? | 130 | 1,000 ml. blood | 60 | 80/50 | 110 | Initial improvement. Died 9 hours later |
| 10 | 71 | Oesophagectomy. Collapse 2nd day. Coma. Dyspnoea. Moribund | 0/0 | 90 | 1,000 ml. blood 500 ml. dextran | 55 | ? | 90 | Slight response to transfusion. Died 30 minutes later |
| 11 | 62 | Partial gastrectomy. Peripheral circulatory failure 18 hours post-operatively. Moribund | 90/? | 130 | 1,500 ml. blood. 500 ml. dextran | 75 | 120/60 | 130 | Fair clinical response. Became conscious but relapsed. Terminal hyperpyrexia. Died 10 hours later |
| 12 | 27 | Ileus and intestinal obstruction following perforated appendix. Peripheral circulatory failure | 65/55 | 124 | 1,000 ml. blood | 30 | 100/60 | 124 | Immediate laparotomy and enterostomy. (local analgesia). Initial improvement. Died 5 days later |

condition and he became conscious. Duodenotomy and the suture of bleeding vessels were performed. Post-operatively his condition was good, but he developed a duodenal fistula. After a subsequent partial gastrectomy he gradually deteriorated, and died in four days.

*Case 2.*—A woman aged 60 was undergoing abdomino-perineal excision of the rectum for carcinoma when she suffered a torrential haemorrhage from the perineal wound. Blood pressure rapidly became immeasurable and the respiration all but failed. Artificial ventilation with oxygen was instituted and intra-arterial transfusion begun in the right common iliac artery. After the rapid infusion of 1,000 ml. of blood, the site of administration was changed to the left radial artery to allow the operation to proceed. A further 1,500 ml. of blood was given by this route. Left brachial plexus block was performed at the end of the operation. Next morning the blood pressure was 125/90 mm. Hg; pulse rate 80. The patient was rational and felt well. The left hand was normal apart from slight blanching of the finger-tips, which soon improved. She made a complete recovery.

In two cases there was apparently marked cardiac insufficiency.

*Case 3.*—A woman aged 61 in whom mesenteric embolus had been diagnosed. On examination, dyspnoeic at rest, rales at lung bases, heart enlarged to left, pulse rate 100, auricular fibrillation, blood pressure 116/60 mm. Hg. She was dehydrated. A slow intravenous drip of glucose-saline was begun pre-operatively. Laparotomy revealed gangrene of terminal ileum, caecum, and ascending colon. Progressive fall in blood pressure despite slow intravenous drip of dextran and blood (Fig. 2). Blood pressure not obtainable 35 minutes after induction. Good response to ouabain, 0.25 mg. intravenously, but not maintained. Further fall of blood pressure to zero, at 70 minutes. Patient cold and pale, aortic pulsation feebly palpable. Intra-arterial transfusion, 300 ml. in five minutes, produced a dramatic response. A further 350 ml. given during next 20 minutes with sustained improvement. Hemicolectomy was completed. The circulation in the hand was normal three hours post-operatively. The patient made a complete recovery. The collapse at operation was thought to be due to a combination of reduced circulating blood volume and insufficient coronary blood flow. The risk of precipitating congestive heart failure indicated the use of the intra-arterial route for rapid transfusion.

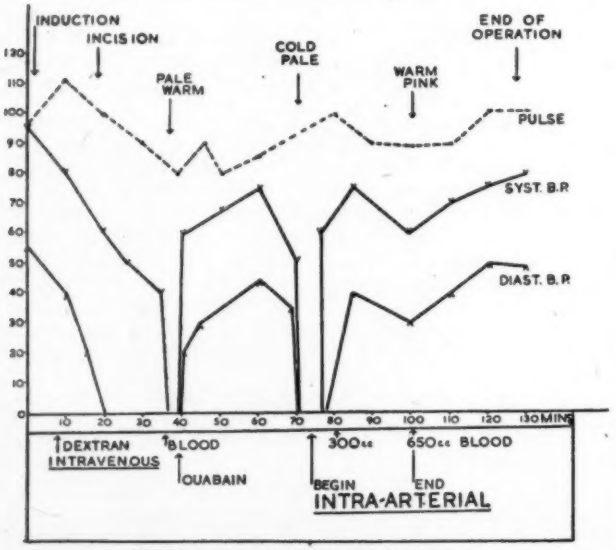


FIG. 2.—Operative record of Case 3.

*Case 4.*—A man aged 68 had abdominal pain and distension for 54 hours, and perforated peptic ulcer was diagnosed. He was gravely ill, cyanosed, with evidence of heart failure and pulmonary oedema. After the intra-arterial transfusion of 1,000 ml. of blood his general condition was much improved. The pulmonary oedema was less. Treatment by continuous gastric aspiration was decided upon. His condition gradually deteriorated and death occurred 24 hours later. Necropsy revealed a volvulus of the small intestine.

Three moribund patients, suffering from peritonitis after perforation of a duodenal ulcer 24 hours or more before admission, were treated with intra-arterial blood transfusion.

*Case 5.*—A woman aged 42 had a perforation of a large acute duodenal ulcer, with gross peritoneal soiling. On admission she was collapsed, pulseless, cyanosed, and dyspnoeic; apex beat 140, blood pressure unobtainable. Continuous oxygen and intravenous therapy with blood was instituted immediately without improvement. Thirty-five minutes later an intra-arterial blood transfusion was begun in the left radial artery. Subsequent progress is shown in Fig. 3. On the first post-operative day the systolic blood pressure was only 70 mm. Hg. Urine output was 120 ml. The left hand was blue and cold. Left brachial plexus block was performed and 0.2% procaine given intravenously. By the second day the blood pressure was 104/70 mm. Hg. The urinary output was 180 ml. The left hand was pink and warm except for the first and second fingers. The urinary output gradually rose to 1,700 ml. on the sixth day. The blood urea had risen to 390 mg. per 100 ml. on the fifth day, but thereafter fell to normal. The left hand recovered completely and the patient was discharged from hospital on the 23rd post-operative day. The extremely satisfactory response to intra-arterial transfusion was

followed by a deterioration in condition (Fig. 3), as operation was delayed. We feel that a decision to operate should be made as soon as there are signs of response to the intra-arterial transfusion, and the theatre prepared so that the operation can begin immediately the patient's condition warrants it. Delay may result in the optimum benefit being lost.

*Case 6.*—In this case, that of a woman aged 51, operation was also delayed (Fig. 4). There was a good response to intra-arterial transfusion, but the delay probably accounted for her deterioration during operation.

*Case 7.*—A girl aged 19 was comatose on admission with no recordable blood pressure. She regained consciousness and her condition improved; but she became suddenly dyspnoeic during the transfusion and died. Necropsy did not help to find the cause of this.

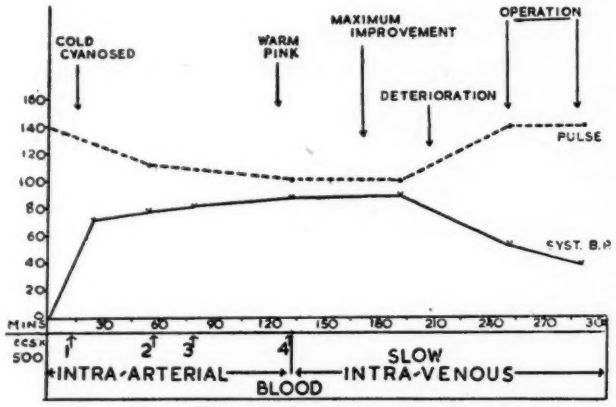


FIG. 3.—Pre-operative and operative record of Case 5.

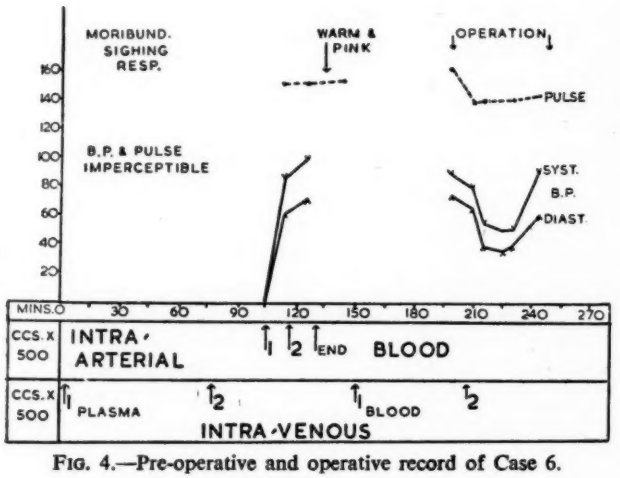


FIG. 4.—Pre-operative and operative record of Case 6.

TABLE III.—*Final State of Circulation in Limb Compared with Response to Transfusion*

| Case No. | Response to Transfusion | Outcome | State of Limb |
|---|---|---|---|
| 1 | Good | Died 7 days later | Normal |
| 2 | ,, | Recovered | Initial blanching of fingertips. Return to normal |
| 3 | ,, | ,, | Hand dusky for 3 hours. Rapid return to normal |
| 4 | ,, | Died 24 hours later | Hand dusky. Rapid return to normal |
| 5 | ,, | Recovered | Hand cold and cyanosed for 24 hours. Completely recovered, though nail of index finger separated |
| 12 | ,, | Died 5 days later | Hand dusky for 3 hours. Rapid return to normal |
| 6 | ,, | ,, 12 hours later | Hand dusky but circulation satisfactory |
| 8 | ,, | ,, 8 ,, ,, | Hand cyanosed. Circulation fair |
| 9 | Fair | ,, 9 ,, ,, | Hand cyanosed and cold |
| 11 | ,, | ,, 10 ,, ,, | ,, ,, ,, |
| 7 | Slight | ,, during transfusion | Cyanosed and cold |
| 10 | ,, | ,, 30 min. later | ,, ,, ,, |

Cases 8–12 showed a gross hypotension and circulatory failure at some stage during the post-operative period.

Most were practically moribund, and intra-arterial transfusion was given as the only means of averting death. The response varied with the severity of the circulatory collapse, but was often good. One patient (Case 12) was improved enough to permit an emergency enterostomy for relief of post-operative intestinal obstruction, but, despite a good initial recovery, he died of bronchopneumonia five days later.

Table III correlates the state of the circulation in the limb used for intra-arterial transfusion with the response to transfusion and ultimate clinical progress. A temporary cyanosis of the hand or forearm was common, but the circulation improved rapidly in those cases showing general recovery. In only one case (No. 5) was there any grave doubt, but brachial plexus block and intravenous procaine gave improvement, and once her general condition became better there was no further cause for anxiety.

## Conclusions

The complete recovery of even two patients out of ten suffering from extreme and apparently hopeless non-haemorrhagic shock, and the temporary improvement obtained in others, at least two of whom (Cases 4 and 8) might have recovered had operation been performed, seem to justify the use of intra-arterial transfusion in such cases. A respite is given to the patient, during which definitive treatment is made possible, which may lead to recovery.

When surgery is contemplated a decision must be made to operate as soon as enough benefit is obtained from the transfusion; delay may result in the optimum state being lost owing to subsequent deterioration in the patient's condition.

In purely haemorrhagic shock, normal circulatory levels will be more certainly and rapidly restored by intra-arterial transfusion than by the intravenous route, less blood should be needed, and operation can be undertaken promptly. This may prove of great value in certain cases—for example, massive gastro-intestinal haemorrhage, in which delay in waiting for improvement to occur inevitably involves the risk of further bleeding.

## Summary

Twelve cases in which intra-arterial transfusion was given are presented. The technique of intra-arterial transfusion is described. A review of the literature shows that haemorrhage has formed the chief indication for the use of the method. The possible value of the treatment in the resuscitation of patients *in extremis* from other forms of shock is discussed.

We wish to thank the surgical staff of the Royal Victoria Infirmary, Newcastle-upon-Tyne, for their ready co-operation, assistance, and interest. Dr. M. H. Armstrong Davison has also taken an important part in the care of these patients.

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# LABORATORY ASPECTS OF COMBINED ANTIBIOTIC TREATMENT

BY

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Since Ungar's observation in 1943 that penicillin and sulphonamides enhance each other's action, the subject of synergism and antagonism between antibacterial substances has received much attention and has recently been extensively reviewed by Garrod (1953). Tests have been made both *in vitro* and *in vivo*, and it is certain that some interaction between antibiotics exists and is likely to be therapeutically important. Clinical experience, though limited, confirms this view; on the one hand, it appears that in the treatment of enterococcal endocarditis a combination of penicillin and streptomycin is more efficient than either drug alone (Hunter, 1950; Robbins and Tompsett, 1951; Cates *et al.*, 1951), and, on the other hand, in pneumococcal meningitis, penicillin and aureomycin used together are less effective than penicillin alone (Lepper and Dowling, 1951).

Interaction occurs in at least three of the manifestations of the antibiotic action: inhibition of growth, lethal effect, and emergence of resistant variants. Growth-inhibition tests are simple to perform, but when used to investigate the combined action of antibiotics often fail to correlate with findings *in vivo* (Jawetz, Gunnison, Speck, and Coleman, 1951; Chopra and Gupta, 1951; Bliss *et al.*, 1952). The estimation of the bactericidal effect of a pair of drugs, as opposed to bacteriostatic effect, is much more laborious, but interaction shown in this way may have more therapeutic significance (Hunter, 1950; Gunnison, Jawetz, and Coleman, 1950; Garrod, 1953). The emergence of resistant variants is also bound up with bactericidal action. The present paper records an investigation of the lethal action of combinations of antibiotics, using a technique simpler than those previously described. The terms synergism and antagonism are defined as follows: a combination of drugs is synergistic when its lethal effect is greater than that of the more lethal drug alone, and antagonistic when its effect is less. Synergism, defined in this way, includes the term "additive" described by other authors. There may, of course, be no interaction, in which case the effect of the more lethal drug is dominant.

A number of different methods have been used in studying the bactericidal effects of mixtures of antibiotics. Generally, complete viable counts have been made at intervals on cultures containing several different concentrations of antibiotics. In order to carry out testing on a larger scale, some workers have used simplified viable counts (Bigger, 1944; Nichols, 1948; Rantz and Randall, 1952), and others the turbidimetric estimation of growth from surviving bacteria (Thomas and Hayes, 1947; Burnell and Kirby, 1951). All these methods are unsuitable for routine testing in a busy clinical laboratory. The simplified viable count method of Martin *et al.* (1952), recommended by Garrod (1953), tests the action of a pair of antibiotics at *one* concentration only. This is likely to be misleading, as there are reports that concentrations are important (Hobby and Dawson, 1946; Bliss *et al.*, 1952). The conditions under which antibiotics act in the body are varied, and it is probable that when a patient receives two drugs their relative concentration fluctuates widely.

Agar diffusion methods used to detect inhibitory levels have the great advantage of allowing a range of relative concentrations to be tested easily, and as they are also widely employed for routine sensitivity tests it is not surprising that attempts have been made to show interaction by such methods (Peyré and Velu, 1952; King *et al.*, 1953; Garrod, 1953). These attempts have, however, been based on interactions at the inhibitory level, and we believe that the appearances of inhibition on solid media can give misleading information. A further step is required to show whether the growth one sees is alive or whether in fact it has been killed. The technique we have used is an agar diffusion method amplified by a simple form of sampling to reveal the lethal action of the antibiotics.

## Method

The method used is the one described in detail by Elek and Hilson (1953), and consists of a transfer of organisms from the surface of the original medium containing antibiotics to the surface of a fresh medium free from drugs. The transfer is made in much the same way that a rubber stamp transfers ink from a pad to a piece of paper: the stamp consists of a cylindrical block of wood with furnishing velvet glued to one surface.

Plates were prepared in a manner similar to the paper disk method of sensitivity testing described by Fairbrother and Martyn (1951). Disks (6 mm. in diameter) were cut out of Ford 428 white blotting-paper with an office punch. The concentrations of the antibiotics used were: penicillin G 500 units per ml., except for enterococci, when a concentration of 50,000 units per ml. was used; streptomycin, 1,000 μg. per ml.; chloramphenicol, 5,000 μg. per ml.; and aureomycin, 12,500 μg. per ml. A well-dried agar plate was flooded with a young broth culture which was just faintly turbid and provided the smallest inoculum capable of producing a confluent growth.

The test for antagonism was set up as follows. Three equidistant points were chosen on the inoculated plate (Fig. 1a). The first received a disk saturated evenly with antibiotic A, the second received a disk similarly treated with antibiotic B, while on the third point two similar disks (A and B) were superimposed. Synergism was tested by placing two disks close enough together to produce overlapping of their zones of inhibition (Fig. 2a). After 18 to 24 hours' incubation at 37° C., the appearances due to inhibition of growth were noted. A velvet stamp, previously sterilized by autoclaving, was then pressed evenly on the surface of the plate (the "primary" plate) and then pressed similarly on the surface of a sterile plate (the "replica" plate) which was incubated overnight.

### Interpretation

The appearances of *inhibitory* effects on the primary plates could not be interpreted reliably. For example, "tongues" of growth were often seen between two disks, suggesting antagonism, but the replica plates showed that sometimes the "tongues" contained no living organisms. Furthermore, areas free from growth were frequently shown to contain many viable bacteria.

The appearances of *bactericidal* interaction which the replica plates revealed were, however, clear-cut. Typical findings on primary and replica plates are illustrated. Fig. 1 shows what is seen when two drugs are antagonistic: the

zones of inhibition produced by drugs A and B on the primary plate are similar, but the replica plate shows that A has killed all the organisms within its zone, while B has allowed almost complete survival. The inhibition zone due to A and B together on the primary plate resembles that of either alone, which would suggest that there has been no interaction. However, the replica shows that the expected lethal action of A is absent, and therefore the combination of A with B is antagonistic. Synergism is illustrated in Fig. 2. The bactericidal action of A extends beyond its expected radius in the area where C is also present. In other words, a sublethal concentration of A becomes lethal when the organisms are also affected by C. This is also shown by the flattening of the contour where the zone edges meet.

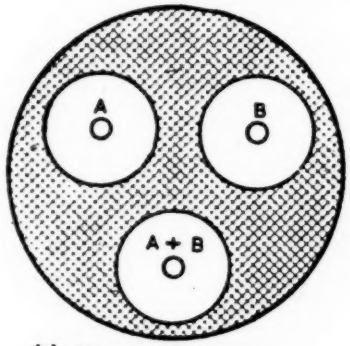

FIG. 1.—Antagonism.

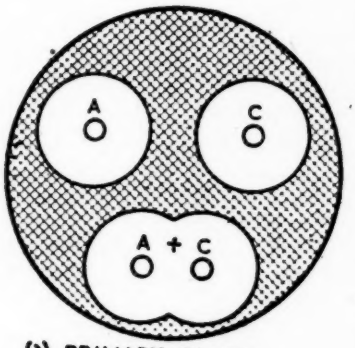

FIG. 2.—Synergism.

## Results

The methods just described were used, and 65 strains of common pathogens were tested with three pairs of antibiotics: penicillin with chloramphenicol, penicillin with aureomycin, and streptomycin with chloramphenicol. The organisms consisted of 28 strains of *Staph. pyogenes* from human lesions, 17 strains of *Bact. coli* from urinary infections, 10 strains of enterococci from cases of subacute bacterial endocarditis, and 10 strains of haemolytic streptococci (Groups A, B, and C). The results are summarized in the Table, from which some consistency in behaviour can be seen for each pair of antibiotics. The combination of penicillin with either chloramphenicol or aureomycin was antagonistic, or showed no interaction, while streptomycin with chloramphenicol was synergistic, or showed no interaction. These general rules appear to be broadly independent of the species of organism.

*Interactions After 18 to 24 Hours*

| Organism | No. | Penicillin + Aureomycin | | | Penicillin + Chloramphenicol | | | Streptomycin + Chloramphenicol | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | S. | N.I. | A. | S. | N.I. | A. | S. | N.I. | A. |
| *Staph. pyogenes* | 28 | 0 | 4 | 24 | 0 | 9 | 19 | 21 | 7 | 0 |
| Haem. strep.: | | | | | | | | | | |
| Group A .. | 5 | 0 | 3 | 2 | 0 | 2 | 3 | 0 | 5 | 0 |
| „ B .. | 3 | 0 | 1 | 2 | 0 | 1 | 2 | 1 | 2 | 0 |
| „ C .. | 2 | 0 | 0 | 2 | 0 | 0 | 2 | 2 | 0 | 0 |
| „ D (endocarditis) | 10 | 0 | 4 | 6 | 0 | 1 | 9 | 4 | 6 | 0 |
| *Bact. coli* (urinary) .. | 17 | 0 | 14 | 3 | 0 | 17 | 0 | 10 | 7 | 0 |
| Total .. | 65 | 0 | 26 | 39 | 0 | 30 | 35 | 38 | 27 | 0 |

S. = Synergism. N.I. = No interaction. A. = Antagonism.

It must be stressed that the results were obtained by incubating the primary plates for 18 to 24 hours before replica plating. Jawetz, Gunnison, and Speck (1951), using one strain of *Str. pyogenes* and one strain of *Klebsiella pneumoniae (Bact. friedländeri)*, reported that streptomycin and chloramphenicol were synergistic after 24 hours' incubation, but antagonistic during the first 12 hours. The earlier findings correlated best with their *in vivo* results, which led them to conclude that they may be more significant therapeutically. We therefore retested six strains of staphylococci and five strains of *Bact. coli* after six to eight hours' incubation of the primary plates. Tested in this way, streptomycin with chloramphenicol was antagonistic with all six strains of staphylococci and with four out of the five *Bact. coli* strains, which contrasts with the synergism found after overnight incubation. Penicillin with aureomycin, tested at the earlier time, showed antagonism or no interaction, the same as was found at 18 to 24 hours' incubation.

## Discussion

On the whole the findings with the method presented here agree with those obtained by other techniques. The antagonism of penicillin and aureomycin has been shown with several different organisms (Gunnison, Coleman, and Jawetz, 1950; Gunnison, Jawetz, and Coleman, 1950; Hunter, 1950), and the antagonism of penicillin with chloramphenicol has also been previously reported (Jawetz, Gunnison, Speck, and Coleman, 1951; Burnell and Kirby, 1951). These two combinations were, however, found to be synergistic with one strain of *Salm. typhi* (Price *et al.*, 1949) and one strain of *Proteus vulgaris* (Jawetz *et al.*, 1952). It has also been suggested that the results depend on the concentrations of the drugs used (Bliss *et al.*, 1952).

Streptomycin and chloramphenicol have been reported as synergistic with 6 out of 33 strains of *Staph. pyogenes*, there being no interaction with the remainder (Rantz and Randall, 1952). Other workers have obtained variable results according to the organism tested or the concentration of drugs used (Jawetz *et al.*, 1952; Bliss *et al.*, 1952). In general, our results agree with those of Jawetz, Gunnison, and Speck (1951), in that this combination was often synergistic after 18 hours' incubation, though antagonistic during the first few hours.

Jawetz and his associates have come to some general conclusions about the behaviour of antibiotic interaction (Jawetz *et al.*, 1952). They believe that antibiotics may be grouped into bactericidal (group 1) and bacteriostatic (group 2) drugs, and suggest that pairs of group 1 are synergistic, while group 1 and group 2 drugs together are antagonistic. They point out, however, that this is only a general rule, to which there are exceptions, and that results for a given organism with any pair of antibiotics cannot be forecast. Hitherto the number of bacterial strains tested has been severely limited by the laborious nature of the techniques required. As a result of our findings with a comparatively large number of strains of different species of bacteria, we can confirm that group 1 and group 2 drugs may be antagonistic during the early period of their action together. With continued incubation up to 24 hours, penicillin and aureomycin may remain antagonistic or may no

longer show interaction; under the same conditions streptomycin and chloramphenicol not only lose their initial antagonism, but with some organisms become synergistic. Unlike some workers (Jawetz *et al.*, 1952; Bliss *et al.*, 1952), we have not found at 18–24 hours that a pair of antibiotics will be synergistic with one organism and antagonistic with another. In our experience any pair of antibiotics will react at this time in the same way, varying only in degree with different organisms. We therefore believe that a limited forecast can be made of the behaviour *in vitro* of a pair of antibiotics when tested against any organism. The value of such a forecast in controlling therapy cannot yet be assessed, since further knowledge of the correlation between laboratory and clinical findings is needed.

Before any prediction can be made of the probable correlation between laboratory and clinical results several difficult questions have to be considered. The first is the problem of the relative importance of bacteriostatic and bactericidal action of antibiotics in the body. The paramount importance of the former mode of action in most forms of infection was not questioned until the combined action of antibiotics was investigated. It then became apparent that the results of testing bacteriostatic activity *in vitro* agreed less well with animal experiments than did the results of tests based on bactericidal action, and the idea has grown up that the lethal activity of antibiotics is the more important *in vivo*. Concentrations used in tests of combined lethal activity have, however, been closer to those attained in the body than the sub-inhibitory levels usually employed in tests based on combined bacteriostatic action, and this may explain some of the divergent results. There can be no doubt that the pattern of interaction alters with time. Jawetz and his colleagues suggest that early readings are of clinical importance, although other workers came to the opposite conclusion (Ahern *et al.*, 1952). Since antibiotic treatment is usually prolonged, we feel that results after 24 hours' contact with the drugs are more likely to be significant. It may even be that results observed after still longer periods are of greatest value. Finally the synergistic lethal action of two antibiotics by allowing fewer survivors may lessen the chance of the emergence of resistant variants. There can be no definite answer to these questions until more work is done to correlate *in vitro* and clinical findings. The method described here may help to serve this purpose.


### Summary

There is both experimental and clinical evidence that two antibiotics used simultaneously may be more efficient (synergistic) or less efficient (antagonistic) in their action than either drug used alone.

A simple method suitable for routine diagnostic work is described. It reveals interactions of the bactericidal effect of antibiotics *in vitro*. Sixty-five strains of common pathogens were tested against three pairs of antibiotics. Penicillin with either chloramphenicol or aureomycin generally showed antagonism. Streptomycin with chloramphenicol was synergistic. These results refer to interaction after 18 to 24 hours. The only exceptions to these findings were that no interaction occurred.


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# CLINICAL TRIAL OF METHIMAZOLE IN TREATMENT OF THYROTOXICOSIS

BY


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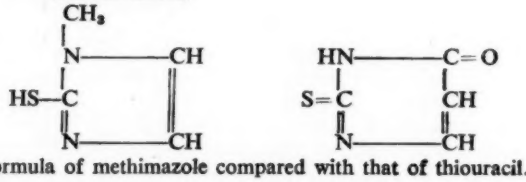
The history of the drug treatment of thyrotoxicosis dates from Chesney's discovery in 1928 that rabbits fed exclusively on cabbage became myxoedematous and developed goitre.[1] Thiouracil was introduced to clinical medicine in 1943 in a paper by E. B. Astwood,[2] and in 1949 Stanley and Astwood[3] reported that 1-methyl-2-mercaptoimidazole, now known as methimazole, was the most active antithyroid drug they had encountered. Methimazole has a basic ring structure of five atoms. This ring contains two nitrogen atoms connected through a carbon atom to which is attached a sulphur atom. This chemical grouping –N–CS–N–, which is common also to the six-membered ring of the thiouracils, is thought to be responsible for the antithyroid activity of the drug (see Formula).

1-Methyl-2-mercaptoimidazole (Methimazole) 2-Thiouracil



Formula of methimazole compared with that of thiouracil.

The normal thyroid gland selectively removes iodine from the blood plasma and converts it into thyroxine. This function is inhibited by antithyroid drugs, which block the formation of di-iodotyrosine within the gland.[3,8] Using the degree of block produced as an index of antithyroid activity, Stanley and Astwood have estimated in man the ability of the different antithyroid drugs to block, in the gland, the conversion into thyroxine of a test dose of radioactive iodine, and thus estimated the clinical potency of each drug.[4] In experiments of this type they found methimazole one hundred times more effective weight for weight than thiouracil.[3] The actual figures published are set out in Table I.

In general clinical use methimazole is 20–50 times more effective weight for weight than compounds of thiouracil. In man a single dose of 5 mg. of methimazole almost completely inhibited the accumulation of radioactive iodine by the gland for nearly 24 hours.[3] In

TABLE I.—*Relative Activities of Various Antithyroid Drugs Compared in Man*[3]

| | |
|---|---|
| 2-Thiouracil | 1 |
| 6-Methylthiouracil | 2 |
| 6-*n*-Propylthiouracil | 0·75 |
| 2-Mercaptoimidazole | 10 |
| 1-Methyl-2-mercaptoimidazole | 100 |

another investigation in mice, methimazole was found to be seven times more toxic weight for weight than thiouracil.

### Clinical Material

This report deals with 44 patients treated with methimazole since January, 1950. Of these, 34 were either untreated cases of thyrotoxicosis or cases which had relapsed after previous drug treatment with methylthiouracil. In the remainder methimazole was used in maintenance dosage following control with methylthiouracil.

The diagnosis of thyrotoxicosis is essentially clinical. In this series the diagnosis was made clinically and confirmed by estimation of the basal metabolic rate. None of the patients had a B.M.R. of less than +15% before treatment. Most of the classical signs of thyrotoxicosis were present in all the cases, and, of the only two who had neither exophthalmos nor goitre, one had a B.M.R. of +88% and the other of +22%. The latter patient had lost 18 lb. (8.2 kg.) in weight, which has been regained with treatment. Estimation of the B.M.R. was found to be a convenient method of following the progress of treatment, and it agreed closely with an independent estimation of the severity of the clinical state in two-thirds of all the tests performed in relation to this series.

In assessing the results of treatment the patients were regarded as euthyroid when all the signs and symptoms of thyroxine intoxication had disappeared and when the B.M.R. was within normal limits. The last sign to disappear was usually tachycardia. The pulse rate was taken to be within normal limits when it was recorded in the out-patient department as under 80 beats a minute without previous rest. In three cases a rate of 84 was accepted as normal. These patients required rest to bring the pulse rate below 80, but were otherwise symptomless.

The patients were treated initially in hospital for two to three weeks, and then either went to the convalescent home for a similar period or were allowed to return home. Thereafter they were seen frequently in the out-patient department.

The 34 cases of thyrotoxicosis comprised 28 women and six men. Their ages varied from 22 to 77 years, with a mean of 45 years 9 months.

The symptoms had been present on the average for eleven months, and the average increase in the B.M.R. was +44.6%. Fourteen cases were classified as mild (average B.M.R. +27%), 14 were classified as of moderate severity (average B.M.R. +48.0%), and six were classified as severe (average B.M.R. +74.5%). This distinction into groups was based on the severity of symptoms, together with the B.M.R. as a secondary consideration, and, although it is difficult to state in words the criteria for inclusion into each group, the clinical distinction will be recognized by all (Table II).

Four cases had had previous treatment with methylthiouracil and had relapsed; these were all mild cases. Five patients had no goitre, eight had a nodular goitre, and the remaining 21 had a diffuse thyroid enlargement. Twenty-six patients had exophthalmos; it was considered to be severe in six.

TABLE II.—*The Clinical Material*

| Character of Disease | No. | Type of Disease | | Average B.M.R. |
|---|---|---|---|---|
| | | Graves's Disease | Nod. Goitre, Thyrotoxicosis | |
| Mild | 14 | 11 | 3 | +27·2% |
| Moderate | 14 | 10 | 4 | +48·0% |
| Severe | 6 | 5 | 1 | +74·5% |
| Total | 34 | 26 | 8 | +44·6% |
| Average B.M.R. | +44·6% | +46·8% | 36·5% | |

The average age of the patients was 45·8 years. The average duration of symptoms was 10·9 months. Nodular goitre was present in 8.

### Treatment

Methimazole is dispensed as small white tablets slightly larger than a saccharin tablet, each containing 5 or 2 mg. of the drug. The drug is soluble in water at room temperature. The tablets are slightly bitter to the taste, but are not unpleasant to take and were not objected to by the patients. There were no immediate unpleasant side-effects such as nausea or diarrhoea. The drug is excreted in the urine.

The dose adopted was the lower standard dose recommended by the makers. The patients received one 5-mg. tablet three times a day. In two cases an initial dose of 8 to 9 mg. daily resulted in a partial remission of symptoms, but complete control was not obtained until the standard dose of 15 mg. daily was used. Two cases received 20 mg. daily for the short period of two to four weeks, as they were rather slow to respond to the drug. Both were controlled.

As soon as the patient was considered to be euthyroid, a maintenance dose of 5 mg. or less daily was begun. Only one case has required a maintenance dose of greater amount, and this patient received 10 mg. daily.

A complete remission of symptoms was produced in every case save one. This lady was on treatment for two months only, as she failed to attend the follow-up clinic after this. She was initially classified as a severe case (B.M.R. +78%); when last seen she had shown steady and considerable improvement and was classified as a mild case (B.M.R. +23%). She had persistent auricular fibrillation, and died from coronary thrombosis three months after stopping treatment.

One case, following control, was subjected to surgery. This man had moderately severe thyrotoxicosis, a nodular goitre, and angina pectoris. It was felt that a rapid and probably radical cure would be most likely to benefit his cardiac condition. When last seen (February, 1953) he was symptom-free, had no angina, and was back at work as a miner.

### Results

Within three or four days of starting treatment with methimazole the patients noted subjective improvement in their condition, and there was obvious clinical improvement within a week in every case; they were feeling more settled and slept better, while their weight had begun to rise and their pulse to fall.

The average time on methimazole until complete control of the symptoms of thyroxine intoxication was achieved was 56 days. The individual figures varied from 15 to 142 days, and it is interesting to note that all the longer times occurred in cases of Graves's disease. The average time taken to control the nodular goitres was 22 days less than that for the cases of Graves's disease. This may be because the average B.M.R. in the nodular goitres with thyrotoxicosis was some 10 points less initially (+36.5%, as against +46.8% for the cases of Graves's disease), or possibly because of the known tendency of thyrotoxicosis with nodular goitre to wax and wane in severity, and so perhaps be the more easily influenced by treatment.

It is also interesting that the four included cases which had relapsed after methylthiouracil treatment were all easily controlled by methimazole. This is not always the case when other drugs are used in the treatment of relapses.

Along with the obvious clinical improvement induced by methimazole, the pulse rate fell (average of 25 beats a minute), the pulse pressure fell (average of 14 mm. Hg), the weight rose (average 14¼ lb.—6.5 kg.), and the B.M.R. became normal (average fall of 39.9%). The average B.M.R. after control was +4.7% (see Chart).

All the surviving patients were back doing their full work within four months of starting treatment. The average time for the group was two months.

Eighteen patients have stopped treatment. The average duration of this treatment was 29 weeks 6 days (minimum

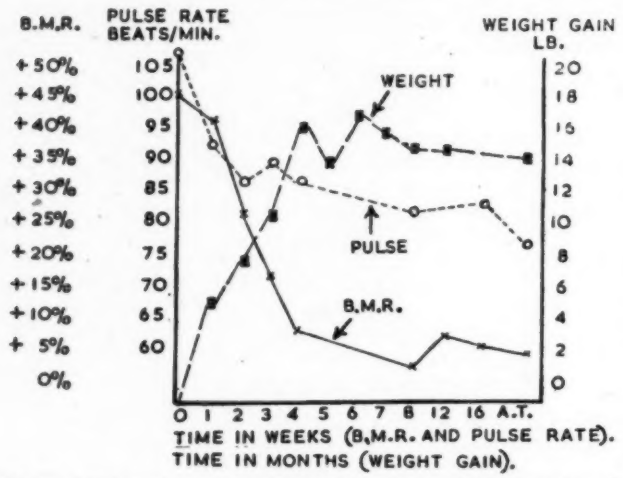



Chart showing response to treatment. The individual results of each patient have been combined to give composite curves of a hypothetical "average" patient. A.T.=After treatment.

7 weeks—maximum 93 weeks), and this is probably too short a time. The average observation period of cures, excluding relapses, was 29 weeks 2 days.

Eight (44%) patients have relapsed. Two of these have been cured by further treatment and have been observed since for six and eight months. The remaining six are still on treatment. Three stopped treatment on their own account and failed to attend the follow-up clinic. The maximum treatment time in this group was 13 weeks. Two patients had a gradual recrudescence of symptoms from the day they stopped treatment and must be regarded as having stopped owing to an error of clinical judgment rather than as true relapses. They restarted methimazole treatment in four and six weeks respectively. One patient recently relapsed after 21 months without treatment.

Thus only three out of the eight had a true relapse following what was thought to be adequate treatment. The average length of time between stopping treatment and the onset of symptoms of the relapse was 22 weeks 6 days.

The final cure rate, then, is at present 12 out of 18—that is, 66%—and these cures have been observed for an average period of 29 weeks 2 days.

Of the other cases two are dead—one from coronary thrombosis and one from carcinoma of the pancreas—one has had a thyroidectomy, and the remaining 13 have been on treatment for an average period of four months. Only one of these has been treated for over nine months.

With methimazole treatment only one goitre has increased in size, 14 have definitely decreased in size, and the remainder have remained the same. Only two patients now have severe exophthalmos as against six before treatment, and 15 are now considered to have no exophthalmos as against eight before treatment (Table III).

These observations on the size of the goitre and the persistence of the exophthalmos are purely clinical. Accurate objective records of the pretreatment size of goitre and the degree of exophthalmos were unfortunately not available in most cases. The findings were therefore classified according to the answers received to the following questions, together with the clinical impressions of the examiner.

Goitre: What has happened to the swelling in your neck since you started treatment?

Exophthalmos: What has happened to your eyes since you started treatment?

Where any doubt existed in the examiner's mind about the accuracy of the answers, the result was recorded as "no change." This method is admittedly inaccurate, but the patient is probably as sound a judge of the state of his or her personal appearance as the doctor, and none seemed to be in doubt about the answers to be given to these questions.

TABLE III.—*The Change in the Eye Signs and in the Goitre with Treatment*

| | Total | Cures | Others |
|---|---|---|---|
| Goitre 0 / Exophthalmos 0 | 12 | 7 | 5 |
| Goitre − / Exophthalmos − | 9 | 3 | 6 |
| Goitre − / Exophthalmos 0 | 5 | 3 | 2 |
| Goitre 0 / Exophthalmos − | 6 | 4 | 2 |
| Goitre + / Exophthalmos 0 | 1 | 1 | 0 |
| Goitre S / Exophthalmos − | 1 | 1 | 0 |

0=No change with treatment. +=Increase with treatment. −=Decrease with treatment. S=Surgical treatment.

Apart from other diseases coinciding with treatment in 20% of cases, the only complications were in the cardiovascular system. Nine patients had complicating cardiovascular disease. In five cases, of whom two had mild cardiac failure, this was the result of the disease and is now cured. In two further cases the diastolic blood pressure has risen with treatment to over 100 mm. Hg, and these two patients must be regarded as cases of essential hypertension masked by thyrotoxicosis. The remaining two patients showed auricular fibrillation. One of these has died of coronary thrombosis, and when last seen after two months' methimazole treatment she was still fibrillating. The other, who when first seen had sinus rhythm, lately presented as a relapse, with auricular fibrillation as the main symptom. He has been under treatment again for eight weeks, and is still fibrillating.

In the 44 people so far treated with methimazole, three unexplained reactions have occurred, but only two of these can properly be attributed to methimazole.

A woman developed a maculo-papular rash on the sixtieth day of treatment. This disappeared within seven days without change in the dosage of the drug or giving specific treatment.

A woman developed a transient papular erythema which came on about half an hour after each dose of methimazole and lasted for about one hour. She was having at this time 20 mg. of methimazole daily in four doses. The rash has not recurred on smaller doses of the drug.

A woman had fever up to 99.8° F. (37.7° C.) with an eosinophilia during the first ten days of treatment, but as this fever started two days before the initial dose of methimazole it cannot be attributed to the drug.

No serious toxic effects have occurred, and in those cases examined there is and has been no evidence of granulocytopenia. The rate of toxic reactions observed in this series was 4.5%.

## Comment

At the present time it is generally accepted that the thyroid gland in thyrotoxicosis is producing excess thyroxine in response to stimulation by excess pituitary thyrotrophic hormone.[5,11] The basic lesion which produces the increased secretion of thyrotrophic hormone has not been defined, but may lie in the pituitary itself, in the hypothalamus, or conceivably in an abnormal reaction of the thyroid gland to the hormone. This last is unlikely, because the hyperplastic tissue of toxic thyroid glands has been found capable of inactivating five to ten times the amount of thyrotrophic hormone that can be inactivated by normal thyroid tissue.[6] Further, in those cases in which exophthalmos is progressing, excess active thyrotrophic hormone can usually be demonstrated in the blood, as well as excess inactive thyrotrophic hormone in the urine, indicating that the stimulus to thyroid gland hyperplasia and hyperfunction comes initially from outside the gland,[7] and, finally, the whole picture can be reversed by destruction of the pituitary.[11]

Clinically the disease seems to be eventually self-limiting in most cases, and from the practical point of view a cure will result provided the body can be protected from the evil effects of excessive stimulation by thyroxine long enough for the basic hormonal upset to subside.

All the modern methods of treatment are attacks on the thyroid gland itself, and are probably basically unsound.

Except in cases in which operation is obligatory, the antithyroid drugs, with their finely graded and only temporary effect, seem to be as good a method of protecting the body from thyroxine excess as any method that has yet been devised,[4] especially as the incidence of carcinoma in Graves's disease is only 0.5% and in toxic nodular goitre less than 1%.[5]

Each antithyroid drug which has been used in the treatment of thyrotoxicosis has been discarded in favour of another as the newcomer has been shown to be more potent in its clinical effect and less noxious to the human body. The aims of treatment are to produce permanent remission of symptoms by means which are at the same time rapid, uniformly successful, and safe.

Methimazole cannot be expected to produce a cure rate higher than any other antithyroid drug, as its antihormonal effect is produced in the same way, at the same point of action, as is the effect of these other antithyroid drugs. The crude cure rate depends upon the length of treatment, the length of time the basic hormonal upset persists, and the length of observation of the cures. The figure of 50 to 60% long-term cures with antithyroid drugs is widely quoted,[10] and it is likely that the final figures in this series will be similar. Methimazole has, however, been shown to act more rapidly than any other drug in common use. It produced a fall in the B.M.R. of 0.8% a day. The average time taken to achieve complete control of symptoms with methimazole is only 60% of the time taken in this clinic with a similar series using methylthiouracil. This has been the general experience of all those who have conducted clinical trials with the drug, and applies also to comparison with propylthiouracil.

Methimazole not only acts more quickly but has a smaller failure rate than methylthiouracil. No case treated here failed to respond to methimazole, nor did any case escape from control once this was established. One out of each 15 cases (7%) treated in this clinic with methylthiouracil was not controlled, and this figure is not abnormal.[11] Propylthiouracil fails in almost twice as many cases as methylthiouracil.[12 13] The failure rate of methimazole in over 1,300 cases treated with the drug is less than 1%.[14] The incidence of toxic effects with methimazole in this series was 4.5%, and none of these effects were serious.

As the usefulness of this drug may well be assessed not so much by its effectiveness as by the incidence of toxic reactions, all the published reports on methimazole in the literature, have been studied,[15–26] and, in addition, the makers of the drug have supplied to me all the information they have collected about its clinical use in 1,350 cases.[14]

The following facts came to light: (1) The toxic effects of methimazole are similar to those of the other antithyroid drugs. (2) The commonest are skin reactions occurring in about 3% of cases. These comprise in the main maculopapular rashes and urticaria. (3) The serious toxic effects described are agranulocytosis, two cases (one fatal),[25 26] a few cases of granulocytopenia, and one case of thrombocytopenic purpura.[22] (4) The reactions have been of such severity as to merit stopping the treatment in 1.5% of cases treated with the drug. The overall incidence of toxic reactions is 4.6%, and that of agranulocytosis 0.15%.[14]

It should be noted that the incidence of reactions is definitely related to dosage. Only a few mild skin reactions have occurred with a dose of less than 20 mg. daily; all the severe reactions have followed doses of more than 30 mg. daily.

It has been shown that 5 mg. of methimazole is effective for nearly 24 hours,[3] and so it is to be expected that 5 mg. eight-hourly will certainly be effective, and there would seem to be little point in raising the dose beyond this, as the rate of response will not be affected and the incidence of toxic reactions will definitely increase. It will be remembered that in the early series reported, using methylthiouracil, the dose was higher than that now normally used, and the incidence of toxic reactions was correspondingly higher than that now expected.[11 15]

The development, maintenance, and progression of the exophthalmos of thyrotoxicosis seem to depend in some way upon the relative balance between production and inactivation of pituitary thyrotrophic hormone, the presence of excess of active hormone in the body producing exophthalmos.[7] Presumably in this series the glands were all able to strike a balance with the hormone production or inactivate more hormone than was produced, and so the exophthalmos did not progress and in many cases has subsided. This is probably a chance finding.

There is no doubt that the lack of enlargement and regression of the goitres in this series is a very real thing. The reason for this finding is unknown. Several tentative hypotheses could be advanced in explanation, but in the absence of any confirmatory evidence these would be valueless. Suffice it to say that the histological picture of glands treated with methimazole and methimazole and iodine does not differ qualitatively from that produced by other antithyroid drugs,[25 27 37] but that in the case reports of other authors those in which the dose used in treatment was of the same magnitude as in our own series tended to confirm our findings, while some of those using larger doses reported occasional enlargements. The majority did not consider the question, as most of their cases were eventually treated by surgery or radioactive iodine therapy.

## Conclusions

Methimazole is a potent antithyroid drug.

It is more effective than the other antithyroid drugs in common use, as regards both the rate of response and the paucity of failures.

It is definitely less toxic than methylthiouracil, and, although slightly more toxic than propylthiouracil, the incidence of severe toxic reactions is of the same order of magnitude as with this latter drug.

Methimazole seems to be the best available preparation for the drug treatment of thyrotoxicosis.

I would like to thank Dr. Robert Mowbray for permission to use his cases for the purposes of this report, and for his interest and help in preparing this paper. Eli Lilly and Company, who supplied the drug for clinical trial under the trade name "tapazole," have been extremely helpful throughout the period of this investigation.

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# TREATMENT OF IRREDUCIBLE INTUSSUSCEPTION

BY

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Until recently the mortality of irreducible intussusception, whatever the method of treatment employed, was depressing. Thus Ladd and Gross (1941) stated: "In any large series of cases there will always be some individuals for whom resection of an intussusception must be employed. In babies under 1 year of age this carries an extremely high mortality, averaging around 75% or more." In McNab's (1948) opinion, "as soon as the intussusception in a child becomes irreducible the mortality rate associated with the treatment rises to 80%." In the last few years, however, the picture has changed very considerably; for example, Gross and Ware (1948) report 11 recoveries in 14 resections, Aird (1949, 1952) 13 survivals from 17 resections, and White and Dennison (1952) 12 recoveries in 16 cases treated by ileocolostomy.

As Aird remarks, these improved results are having a most beneficial effect upon the morale of surgeons, and if it is felt that resection is at least reasonably hopeful as a method of treatment the surgeon is more inclined to proceed to it at a stage when the child has not been intoxicated by the squeezing of infected material into its circulation. It is perhaps permissible to suggest that the time has now come when a child who has to have an irreducible intussusception resected should be expected to survive. The purpose of this communication is to present a method of dealing with these cases by resection and early restoration of bowel continuity, a method which has been found safe and satisfactory, and which, for reasons that will be discussed, is believed to have several advantages over previously described methods. The technique employed was initially used by me in dealing with the first irreducible case in this present series, and, with minor variations, it has been used for all subsequent cases.

## Material

In this report are presented the results of nine cases of irreducible intussusception treated by this method, with eight recoveries and one death. These cases were treated between January 1, 1951, and December 31, 1952. During the same period 82 cases of reducible intussusception were treated by operative reduction with no deaths.

A further 12 cases which occurred are not included in this series for the following reasons: six cases had intussusceptions on admission which underwent spontaneous reduction shortly after admission without operation and without mortality; six cases belonged to the subacute or chronic group with symptoms lasting from 5 to 35 days: operative reduction of these was performed with no deaths.

TABLE I.—*Distribution of Reducible Cases According to Time Interval Between Onset of Symptoms and Admission to Hospital*

| 0–6 Hours | 6–12 Hours | 12–24 Hours | 24–48 Hours | 48–72 Hours | 3–5 Days |
|---|---|---|---|---|---|
| 18 | 11 | 19 | 22 | 6 | 6 |

TABLE II.—*Results in All Cases Operated Upon Between January 1, 1951, and December 31, 1952*

| | No. | Deaths | % Age Mortality |
|---|---|---|---|
| Reducible .. .. | 82 | 0 | 0 |
| Irreducible .. | 9 | 1 | 11·1 |
| Total .. .. | 91 | 1 | 1·09 |

In the total of 103 cases accepted for admission the overall mortality was 0.97%.

It must be emphasized that in our opinion results of this kind can be achieved only if there is close and continuous co-operation between surgeon and paediatrician: the treatment of these children demands not only a competent surgical technique but also skilled, devoted, and often prolonged and arduous post-operative medical and nursing care. The majority of these children have been operated upon by four members of the surgical staff of the Royal Victoria Infirmary who are of senior status and who are at the same time engaged in general surgical practice. We believe that this policy has been an important factor in lowering mortality.

## Diagnosis

Little can be added to the admirable account already given by Morrison and Court (1948) from this school. It is, of course, a matter for regret that the diagnosis should have been delayed so long in some of our cases, but the delay has often appeared due not so much to lack of care or neglect on the part of the family doctor as to a failure to consider the possibility of intussusception at all. The reason for this is undoubtedly the comparative rarity of the condition, and it is possible that a policy of closer integration between consultant and practitioner as advocated by Spence and Court (1950) would diminish the number of late cases occurring. Lateness in diagnosis is, however, not the only factor responsible; there is no constant relationship between duration of symptoms and irreducibility, and, as White and Dennison have pointed out, another factor of equal if not greater importance is the degree of fixation or otherwise of the caecum and ascending colon. A mobile colon will allow the apex of the intussusception to travel onwards with relatively little interference with its blood supply, and in these cases, even after 24 to 48 hours or longer, the intussusception may be easily reducible and the bowel viable. With a fixed colon, on the other hand, the mesentery of the entering bowel becomes obstructed at an early stage, with consequent oedema and congestion, and these cases may prove irreducible even within the first 12 to 24 hours.

We do not favour the use of diagnostic barium enemata, believing that the manipulations involved have a definite adverse effect on the child's general condition; the occasions on which the diagnosis is in doubt are very few, and in these circumstances we prefer the safety and certainty of an exploratory laparotomy.

## Treatment

These children are ill, dehydrated, and obstructed, and operation should not be considered until an intravenous plasma drip has been erected and is running satisfactorily, and some at any rate of the dehydration has been corrected; this must be done even though it may mean delaying operation for three or four hours, or longer. A nasal catheter must be passed before operation and the stomach emptied and kept empty.

Premedication consists in the administration of 1/480 gr. (0.14 mg.) atropine into the drip for a child under 1 year of age; anaesthesia is induced by nitrous oxide and ether, and maintained by oxygen and ether with some nitrous oxide; mephenesin has been used on occasion. The essentials are that there should be a good airway, that respiration should not be too depressed, and that there should be

adequate relaxation. We think it desirable that the anaesthetist should take an active part in the conduct of the case throughout, in the decision regarding the best time to operate, and in the management of any post-operative complications that may occur. The abdomen is opened by a right paramedian rectus-splitting incision; as much of the reduction as possible is performed intraperitoneally; and the mass is then withdrawn from the abdomen, covered with warm saline packs, and gently compressed to try to reduce congestion and oedema. Further attempts at reduction are then made, but as soon as it is evident that these are not going to succeed, or if it is obvious that the bowel is necrotic or gangrenous, then resection is proceeded with. A good deal of experience is required to enable the surgeon to recognize irreducibility at as early a stage as possible; if he does not do so, but persists with attempts at reduction, the bowel is devitalized still further, the child's general condition deteriorates, and it is less well able to withstand the next stage.

TABLE III.—*Cases Treated by Two-stage Resection and Anastomosis*

| No. | Age | Duration | Type | Extent of Resection | Result |
|---|---|---|---|---|---|
| 1 | 4 mths | 42 hours | Ileo-colic | Right hemicolectomy | Satisfactory |
| 2 | 7½ ,, | 10 ,, | Ileo-ileal | 5 in. (12·7 cm.) terminal ileum | ,, |
| 3 | 3 ,, | 59 ,, | Ileo-colic | 3 in. (7·7 cm.) terminal ileum; whole colon down to pelvic colon | Died |
| 4 | 2½ yrs | 56 ,, | Ileo-ileal | 9 in. (22·8 cm.) terminal ileum | Satisfactory |
| 5 | 3 mths | 28 ,, | Ileo-colic | Right hemicolectomy | ,, |
| 6 | 11 ,, | 86 ,, | ,, | ,, ,, | ,, |
| 7 | 5 ,, | 77 ,, | ,, | ,, ,, | ,, |
| 8 | 4 yrs | 22 ,, | Ileo-ileal, starting with invaginated Meckel's diverticulum | 12 in. (30·5 cm.) terminal ileum | ,, |
| 9 | 4½ mths | 48 ,, | Ileo-ileo-colic | 8 in. (20·3 cm.) terminal ileum | ,, |

Cases 2 and 8 were operated on by Professor F. H. Bentley; Case 4 by Mr. F. D. Hindmarsh; Case 9 by Mr. D. J. Tibbs; and Cases 1, 3, 5, 6, and 7 by me.

The resection is performed in the usual way and the abdominal wall is closed snugly round the two adjacent limbs of the exteriorized loop; the limbs are not sutured together, nor are they attached to the abdominal wall. After protecting the skin incision, bowel clamps are applied, the devitalized bowel is removed, and a small Paul's tube is tied into each of the two open bowel ends.

The second stage of the operation is performed approximately 48 hours later. The first step is to tie a stout ligature tightly around each limb of bowel between the Paul's tube and the skin surface; the bowel is then cut across just beyond this ligature and the two Paul's tubes with the fringe of bowel around each are removed. The short stumps of bowel, together with the surrounding skin, are then thoroughly cleansed with cetrimide and the skin sutures removed. Having done this, the surgeon rescrubs and proceeds with the next steps of the operation; the abdomen is reopened, and the two limbs of bowel are freed from the abdominal wall and from one another. The terminal inch or so of each limb tends to be rather oedematous and friable as a result of its exteriorization and does not hold sutures well; this short cuff of bowel on either limb is therefore removed and the bowel ends are closed with two layers of continuous catgut sutures; continuity of the bowel is then restored by side-to-side anastomosis. The abdomen is closed in layers. A drain is not used unless there is doubt concerning the viability of the bowel.

Ideally, the best treatment for these cases would be primary resection and anastomosis, but in our experience this procedure has given the worst results. We are averse to using suture methods in the presence of an acute obstruction, and we have found that decompression of the bowel for about 48 hours improves tone, reduces oedema and congestion, and makes it better able to hold sutures. Of even greater importance is the fact that the very ill child cannot stand a primary resection and anastomosis: where this operation has been done in the past, death has been due not to a leakage from the anastomosis but to acute constitutional failure associated with collapse, and in some cases with hyperpyrexia, and it has usually occurred very soon after the termination of the operation. The two-stage operation does the minimum to the ill child, and it defers the "injury" of the anastomosis until the child is better able to withstand it. We have found a 48-hour period between the two stages sufficient, and we like to proceed with the second stage before the Paul's tubes drop out, with the resultant soiling of the skin and possible infection of the wound. We have not used a "spur" type of double-barrelled enterostomy; we dislike this procedure in infants because of the occasional difficulties associated with its closure and the consequent delay in re-establishing normal bowel function. The average length of stay in hospital in our eight surviving cases was 17.1 days. At the time of discharge, in each case, the wound was healed and bowel function normal.

It has often been stated that while vascular obstruction will lead to gangrene of the inner and middle layers of an intussusception the ensheathing layer is not affected and remains viable. In two of our cases, however, this was not so. In Case 3, duration 54 hours, the apex of the intussusception was at the anal margin, and was black and gangrenous. The child was very ill and shocked, with a tense distended abdomen. Operation was performed five hours after admission. Reduction was at first relatively easy, but when the apex had reached the middle of the descending colon—and thus far no force had been used—it was noted that there were multiple greenish-yellow well-demarcated oval necrotic areas about 1.5 cm. in greatest diameter in the ensheathing layer. These areas started below in the upper pelvic colon, and were all situated on the medial wall of the gut, close to the mesenteric attachment. There were narrow bridges of normal-looking bowel between the areas, and the remainder of the bowel circumference also looked normal. As more of the intussusception was reduced, more necrotic areas became visible, and it was therefore decided to resect the whole of the large bowel to a point below the most distal of the visible areas of necrosis. This was done, and 36 hours later continuity of the bowel was restored by a side-to-side anastomosis of ileum to the stump of pelvic colon. The child's condition remained satisfactory for six days, but a faecal fistula then developed owing to giving way of the anastomosis. Repeated attempts were made to close this fistula, but without success, and, despite an unremitting battle, the child eventually died on the sixty-eighth day after admission.

It is probable that the breakdown of the anastomosis was due to interference with the blood supply to the remaining portion of large bowel, although this was not apparent at the time. If this was the case, it is difficult to see what other procedure could have re-established normal bowel function and allowed the child to survive.

In Case 6, duration 86 hours, the apex of the intussusception was in the pelvic colon. It reduced easily at first, but the terminal three inches (7.7 cm.) was irreducible, and the bowel was black and gangrenous. The terminal ileum, caecum, and ascending colon were resected. The reduced part of the ensheathing layer appeared normal at this time, and there had been no tearing of the serosa during reduction. Forty-eight hours later, however, at the second stage, we found three areas of greenish-yellow necrosis in the transverse colon: the most proximal area was 3 cm. from the divided end of the colon, and around it there was a small collection of pus; the most distal area was just proximal to the splenic flexure; and the third area was in the middle

of the transverse colon. Each area was oval in shape in the long axis of the bowel, measuring approximately 2.5 by 1.5 cm., and situated on the medial wall close to the mesenteric attachment; each was sharply circumscribed, and the rest of the bowel appeared normal. A cuff of colon containing the most proximal area was resected, the area near the splenic flexure was oversewn and invaginated with a single layer of continuous catgut suture, and the third area was locally excised and the resultant defect in the bowel wall used as a stoma for the ileo-colic anastomosis. Recovery was uneventful.

These two cases indicate that ischaemic necrosis of the ensheathing layer can occur. We do not believe that the trauma associated with reduction had any part in the production of these changes, and for this reason we are loath to employ any method of primary anastomosis, with or without resection of the irreducible portion of bowel. The possibility of these changes occurring is a further factor influencing the choice of 48 hours as the optimum time interval between the two stages. Delay much beyond this time may be associated with perforation of one of the necrotic areas, with either a generalized or a localized peritoneal infection.

### Post-operative Treatment

Consideration of the detailed management of the post-operative period is outside the scope of this article, but stress must be laid on the great importance of this phase of treatment, and tribute paid to the skill and enthusiasm of our paediatric colleagues, who have supervised the day-to-day care of these children. This care entails attention to the state of the child's nutrition, hydration, and oxygenation; correction of blood electrolyte changes; the use of antibiotics, sedatives, or stimulants as required; and, most important of all, frequent clinical assessments of the child's condition and progress. If these requirements cannot be fulfilled, then the child's prospects of survival are correspondingly reduced.

### Summary

Ninety-one cases of intussusception occurring in infants and young children are presented. Of these cases 82 were reduced at operation with no deaths. Nine cases were irreducible and were treated by a two-stage procedure of resection and early restoration of bowel continuity with one death.

The reasons for employing the two-stage operation are discussed.

Attention is drawn to the possibility of ischaemic changes occurring in the outer layer of the intussusception in late cases.

Stress is laid on the importance of correct pre-operative and post-operative management of these ill children.

It is a pleasure to acknowledge the help received from Sir James Spence and members of his staff, particularly Dr. Donald Court and Dr. Hugh Jackson, in the preparation of this report. I should also like to thank Mr. John Gilmour for his constant encouragement and advice.

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# THE ACCIDENT-PRONE IN GENERAL PRACTICE*

BY

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*From a General Practice*
*Hawick, Scotland*

Accidents are usually regarded as a hospital problem. While investigating the diseases encountered in family practice the importance of this subject to the general practitioner impressed me and seemed worthy of record.

My practice is situated in a small manufacturing town in the Scottish Borders. It is partly rural and partly suburban. The suburban population are mainly employed in the manufacture of high-class hosiery and tweed. These industries are not the cause of many accidents, so it is not of industrial injuries that I write. The extensive rural areas are concerned with sheep farming and, to a less extent, dairy produce. The total population of the area is about 21,000, of whom 17,500 live in the town and about 3,500 in the rural areas. My share of this population is 2,562, and of these 716 live in the country.

TABLE I.—*Population at Risk*

| Age | M | F | Total |
|---|---|---|---|
| 0–4 years | 102 | 102 | 204 |
| 5–14 ,, | 160 | 146 | 306 |
| 15–44 ,, | 515 | 520 | 1,035 |
| 45–64 ,, | 273 | 385 | 658 |
| 65+ ,, | 155 | 199 | 354 |
| Not stated | 1 | 4 | 5 |
| | 1,206 | 1,356 | 2,562 |

Table I shows the age distribution of these 2,562 patients—a distribution which corresponds with what one would expect in a rural district. There is a relative deficit in pre-school and school age groups and an excess in the older age groups, taking Scotland as a whole.

### Accidents Encountered

During the first two years of the National Health Service 401 of those 2,562 patients were involved in 468 accidents. I have classified those accidents according to the type of injury, and for this purpose have adopted the classification used by Lockhart (1950) when he made a survey of the accident cases treated as out-patients or admitted to Stirling Hospital. This permits me to compare hospital figures with those of general practice, which, of course, includes cases treated in hospital or at home.

TABLE II.—*Type of Accident (All Cases)*

| Diagnosis | M | F | Total | Hawick % | Stirling % |
|---|---|---|---|---|---|
| Bruises | 59 | 47 | 106 | 22·65 | 10·13 |
| Sprains and strains | 60 | 47 | 107 | 22·86 | 9·58 |
| Fractures | 32 | 20 | 52 | 11·11 | 19·06 |
| Open wounds | 56 | 16 | 72 | 15·38 | 38·49 |
| Foreign bodies | 19 | 7 | 26 | 5·55 | 8·20 |
| General effects of internal causes | 3 | 5 | 8 | 1·71 | 0·18 |
| Burns and scalds | 17 | 16 | 33 | 7·05 | 4·14 |
| Head injuries | 9 | 5 | 14 | 2·99 | 5·34 |
| Crushing injuries | 8 | 3 | 11 | 2·35 | 2·03 |
| Other forms of violence | 19 | 20 | 39 | 8·35 | 2·85 |
| Total | 282 | 186 | 468 | 100·0 | 100·0 |

*This investigation formed part of the work undertaken while receiving the Ernest Hart Memorial Scholarship of the British Medical Association. I feel it should be more widely known that such scholarships are available to general practitioners who are prepared to do research in general practice.

Table II shows the type of injury encountered. There were 282 accidents in males and 186 in females. In all but two groups accidents in males were the more numerous, the disparity being greatest among open wounds, fractures, foreign bodies, and, to a less extent, among bruises and sprains and strains. In the last two columns my figures are compared with those of Stirling Hospital. It will be observed that general-practice figures are higher for bruises, sprains and strains, burns and scalds, and what are described as "other forms of violence." Hospital figures are higher for fractures, open wounds, foreign bodies, and head injuries—indicating that hospital figures show a bias in favour of severity. My own figures seem to confirm this. Of these cases, 37 were sent either to the Cottage Hospital (32) or to larger hospitals outside my own jurisdiction (5). Twenty-one were fractures, 8 were open wounds, 3 were severe sprains of joints, 2 were extensive burns, 2 were bruises, and one was a severe eye injury.

### Significance of Accidents

Table III shows the significance of accidents encountered in general practice. It must not be assumed that the disability figures indicate the number of days off work or school; in many cases they do, but in others they do not—for example, a person with a Colles fracture may be at work or school with the arm in plaster, but is still regarded as incapacitated. It will be seen that in the males the 282 accidents caused a total invalidism of 1,953 days, with an average recovery rate of 6.9 days. The average recovery rates vary greatly, and suggest, what is true, that the injuries were most severe among those of school age. In Table III these accidents are compared with a number of the more common diseases which cause patients to consult their doctor.

In the male, in the pre-school years, accidents are surpassed in frequency by the common cold, infectious diseases, and skin conditions; and the invalidism caused by accidents is insignificant compared with that from infectious diseases and skin conditions, and is only half that of the common cold. In the 5–14 age group, accidents are exceeded only by the common cold, and the invalidism is much greater than from any other cause. In the 15–44 age group accidents are more numerous and the invalidism greater than in any other group. In the 45–64 age group the number of accidents and the days of incapacity are exceeded only by the number of arthritic and joint conditions. In the 65-and-over group accidents assume the insignificance that they show in the 0–4 group. The average time of recovery is slightly below the average for all causes.

In the female a different picture is seen. In the 0–4 group accidents are exceeded by the common cold and acute infectious diseases both in numerical frequency and in duration of incapacity. In the 5–14 group accidents do not assume the importance shown in the male. In the 15–44 group again their numerical frequency and the resulting invalidism are not comparable to those of anxiety states, skin conditions, and the upper respiratory infections, and are less than with the common cold. In the 45–64 group, accidents begin to be of greater significance and in numbers are surpassed only by the common cold, anxiety states, and arthritic and joint conditions; but the invalidism is still less than that of anxiety states, skin conditions, and arthritis. In the 65-and-over group, however, accidents are numerically inferior to many of the conditions, but are by far the most serious cause of invalidism. The average rate of recovery from accidents is the same as that for the male, but in my series the female rate of 6.9 days is higher than the overall average for the sex, which is 5.28 days. The prolonged recovery rate in the 65-and-over group is due to fractures of the neck of the femur being more common (with me) among the elderly females.

By the inclusion of the grand total of illnesses encountered in the first two years of the National Health Service, along with the resulting invalidism, Table III not only shows the importance of accidents but also illustrates the problem facing the general practitioner and what he should endeavour to reduce. It will be seen that the 4,148 ailments of the female caused an invalidism of 21,908 days, while the 2,810 ailments of the male accounted for 21,464 days. Though the males had fewer complaints, their recovery was more tardy in all age groups except that of 65 and over.

### Seasonal Distribution of Total Accidents

The neighbourhood in which my practice is situated is mountainous, and during the winter months snow and ice-bound roads are a frequent occurrence. The wearing of chains on motor-car wheels is very often necessary. It might be expected that accidents would be more common during this period, but such is not the case. May, June, and July have the most accidents (Table IV). A partial explanation for this is our annual festival, which has been held

TABLE IV.—*Seasonal Distribution of Accidents (Total, 468)*

| Jan. | Feb. | Mar. | Apr. | May | June | July | Aug. | Sept. | Oct. | Nov. | Dec. | N.S. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 30 | 32 | 30 | 41 | 54 | 48 | 54 | 42 | 35 | 36 | 39 | 25 | 2 |

TABLE III.—*Accident and Sickness Invalidism*

| | 0–4 | | 5–14 | | 15–44 | | 45–64 | | 65+ | | Total | | Average Recovery Rate (Days) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | D | No. | D | No. | D | No. | D | No. | D | No. | D | Total | 0–4 | 5–14 | 15–44 | 45–64 | 65+ |
| *Males* | | | | | | | | | | | | | | | | | | |
| Accidents | 25 | 57 | 48 | 518 | 141 | 913 | 52 | 391 | 16 | 74 | 282 | 1,953 | 6·9 | 2·3 | 10·8 | 6·5 | 7·5 | 4·6 |
| Common cold | 54 | 107 | 49 | 183 | 69 | 216 | 39 | 156 | 34 | 106 | 245 | 768 | 3·1 | 2·0 | 3·7 | 3·1 | 4·0 | 3·1 |
| Acute infectious diseases | 36 | 324 | 33 | 259 | 13 | 104 | 7 | 113 | 2 | 28 | 91 | 828 | 9·1 | 9·0 | 7·8 | 8·0 | 16·1 | 14·0 |
| Anxiety states | 8 | 8 | 4 | 7 | 49 | 148 | 31 | 145 | 14 | — | 106 | 308 | 2·9 | 1·0 | 1·8 | 3·0 | 4·7 | — |
| Skin conditions | 36 | 127 | 20 | 168 | 56 | 568 | 24 | 277 | 20 | 64 | 156 | 1,204 | 7·7 | 3·5 | 8·4 | 10·1 | 11·5 | 3·2 |
| Arthritis and joint conditions | 9 | — | 7 | 67 | 77 | 528 | 60 | 461 | 18 | 158 | 171 | 1,214 | 7·1 | — | 18·3 | 9·2 | 7·9 | 33·7 |
| Upper respiratory infections | 7 | 115 | 10 | 140 | 14 | 150 | 13 | 347 | 9 | 117 | 53 | 869 | 16·4 | 16·4 | 14·0 | 10·7 | 26·7 | 13·0 |
| Chronic bronchitis and pneumonia | — | — | 3 | 20 | 4 | — | 2 | 79 | 18 | 145 | 27 | 244 | 9·0 | — | 6·7 | — | 39·5 | 8·1 |
| All causes | 416 | 1,541 | 363 | 2,394 | 994 | 6,870 | 652 | 8,010 | 380 | 2,649 | 2,810 | 21,464 | 7·64 | 3·7 | 6·6 | 6·9 | 12·3 | 7·0 |
| *Females* | | | | | | | | | | | | | | | | | | |
| Accidents | 18 | 58 | 18 | 76 | 60 | 153 | 61 | 402 | 29 | 604 | 186 | 1,293 | 6·9 | 3·2 | 4·2 | 2·6 | 6·6 | 20·8 |
| Common cold | 51 | 99 | 40 | 113 | 107 | 208 | 82 | 310 | 35 | 203 | 313 | 933 | 3·0 | 1·9 | 2·8 | 1·9 | 3·8 | 5·8 |
| Acute infectious diseases | 36 | 409 | 20 | 114 | 14 | 155 | 12 | 144 | 5 | 48 | 87 | 870 | 10·1 | 11·4 | 5·7 | 11·1 | 12·0 | 9·6 |
| Anxiety states | 4 | — | 5 | 6 | 121 | 886 | 80 | 505 | 48 | 231 | 258 | 1,628 | 6·3 | — | 1·2 | 7·3 | 6·3 | 4·8 |
| Skin conditions | 13 | 41 | 26 | 27 | 75 | 269 | 43 | 875 | 15 | 33 | 172 | 1,245 | 7·2 | 3·2 | 1·0 | 3·6 | 20·3 | 2·2 |
| Arthritis and joint conditions | 5 | — | 10 | — | 83 | — | 126 | 1,138 | 64 | 388 | 288 | 2,093 | 7·3 | — | — | 11·8 | 14·3 | 13·0 |
| Upper respiratory infections | 8 | 21 | 16 | 104 | 27 | 255 | 16 | 279 | 14 | 206 | 81 | 865 | 10·7 | 2·6 | 6·5 | 9·4 | 17·4 | 14·7 |
| Chronic bronchitis and pneumonia | — | — | 1 | — | 2 | — | 17 | 63 | 32 | 504 | 52 | 567 | 10·9 | — | — | — | 3·7 | 15·8 |
| All causes | 325 | 1,003 | 310 | 946 | 1,489 | 6,860 | 1,327 | 8,218 | 696 | 4,878 | 4,148 | 21,908 | 5·28 | 3·1 | 3·1 | 4·6 | 6·2 | 7·0 |

D=Duration of disability.

each year since 1514. It celebrates the defeat of the English army by the young men of Hawick the year following the battle of Flodden. This festival starts in May and culminates in three days of intense activity during the first week of June. It is a hilarious occasion and is a potent cause of accidents. This is not the whole explanation, however, since July is also a month of an increased number of injuries.

### The Population Involved in Accidents

These 468 accidents involved 401 patients (239 males and 162 females). Table V shows the age distribution of these people along with the male and female rates as a percentage of the numbers at risk. The overall male/female ratio of

TABLE V.—*Population Involved in Total Accidents*

| Age | No. | | % of Group | | M/F Ratio |
|---|---|---|---|---|---|
| | Male | Female | Male | Female | |
| 0–4 years .. | 22 | 15 | 10·7 | 7·3 | 1·46 |
| 5–14 „ .. | 44 | 16 | 14·3 | 5·2 | 2·75 |
| 15–44 „ .. | 114 | 56 | 11·0 | 5·3 | 2·07 |
| 45–64 „ .. | 43 | 50 | 6·5 | 7·6 | 0·85 |
| 65+ „ .. | 16 | 25 | 4·5 | 7·0 | 0·64 |
| All ages .. | 239 | 162 | 9·3 | 6·3 | 1·47 |

1.47 clearly demonstrates the male proclivity for accidents. The male in the tender years of 0–4 shows his adventurous spirit by a percentage of 10.7; this rises in the 5–14 group to 14.3%, the highest of all the groups. A reduction to 11.0% is seen in the 15–44 group, but middle age is well advanced before there is a dramatic fall to 6.5%, a fall that is more than maintained by the elderly male with 4.5%. The overall percentage in the male is 9.3. The female shows a different picture. The 0–4 female group shows 7.3%, but from 5–14 there is a fall to 5.2%, the lowest figure of all female age groups. Thereafter it rises to 7.6% for 45–64 group, the highest figure, and falls to 7.0% for the 65-and-over group. The overall percentage in the female is 6.3.

This variation between the male and female in the proclivity to accidents is best illustrated by the male/female ratio in each age group. The general male excess is 47%, but the male excess applies only to the under 45 age groups. In the two oldest groups the females have a decidedly heavier rate of accident. In the younger age groups the male rate is relatively greatest in the school age with almost three times that of the female, a 2:1 majority in industrial life, and a 46% excess in the pre-school years. In this series the accident liability shifts from the young male to the elderly female.

During the two years under review 202 men had one accident, 31 men had two accidents, and 6 men had three; 141 women had one accident, 18 had two accidents, and 3 had three. Thus 58 subjects had more than one accident. Table VI analyses these 58 patients according to age group. It will be seen that the young male and the elderly female are again those most often involved.

TABLE VI.—*Age Groups of Those Having Multiple Accidents*

| | 0–4 | 5–14 | 15–44 | 45–64 | 65+ | Total |
|---|---|---|---|---|---|---|
| Males .. | 5 | 1 | 24 | 7 | 0 | 37 |
| Females .. | 2 | 0 | 6 | 11 | 2 | 21 |
| | 7 | 1 | 30 | 18 | 2 | 58 |

Further evidence of a personal proclivity for accidents is furnished by the following facts: (1) Of the 239 males involved in accidents in 1948–50, no fewer than 74 (31%) had one or more accidents in the following two years. (2) Of the 162 females having one or more accidents in 1948–50, 34 (20%) had one or more accidents during 1950–2. These frequency rates are very much greater than the average risk of incurring an accident, and lead me to believe that the accident-prone person does exist.

*Correlation of Accident and Sickness.*—From previous work I was aware of the general sickness rates occurring in my practice, and in order to compare this with my accident cases I extracted the number of separate illnesses suffered by those who had had accidents. Table VII shows that the individual who is accident-prone is also sick-prone.

TABLE VII.—*Correlation of Accident and Sickness*

| | Illnesses per Male | Illnesses per Female |
|---|---|---|
| General population .. .. | 1·90 | 2·20 |
| Those with accident .. .. | 2·43 | 3·47 |
| „ „ more than one accident | 3·22 | 4·43 |

The general population rate of illness was 1.90 per male and 2.20 per female. Those with one accident had 2.43 per male and 3.47 per female. Those who had had more than one accident had even higher sickness rates—3.22 per male and 4.43 per female.

*Town and Country.*—In the present series, of the 716 patients living in the country, 94 (13.1%) were involved in accidents, whereas of the 1,846 living in the town, 307 (16.8%) had accidents.

### Conclusions

Any conclusions I might arrive at concerning accidents must be considered to apply to my area only, unless similar findings have been discovered elsewhere. Many of my findings corroborate what is already known, but, so far, I conclude: (1) That the town dweller suffers more accidents than those who reside in the rural areas. (2) That there seems to be a seasonal distribution of accidents in my area. (3) That, though their number may not be very large, accident-prone persons do exist; and that the accident-prone are also sick-prone. (4) That the male is the more prone in the school and the early industrial age, and, to a less extent, in the pre-school years; and that the period of greatest frequency of accidents is also the period of greatest severity. (5) That the female is more prone than the male after 45 years of age, and that this is also the period of greatest severity of injuries among females.

Finally, I would like to express agreement with the leading article that appeared in the *British Medical Journal* of September 20, 1952 (p. 656), the last passage of which I quote: "It will probably prove more profitable in the long run to discover more about the conditions giving rise to accidents and about the limits of perceptual and motor response of the average person, so as eventually to modify the working environment and reduce the total risk, rather than to pick out the unfortunate accident-prone."

My thanks are due to Dr. Peter McKinlay for much help and advice with the statistical tables, and to my secretary, Mrs. Potts, for her care of my notes.

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The Ministry of Health has issued a booklet entitled "Your Blood and How it is Used to Save Life." It describes simply the composition of blood and the medical conditions which may need treatment by blood transfusion. Its purpose is to answer some of the questions blood donors are often asked. In explaining the great value of blood donations, it states that over half a million bottles of blood are required every year by the National Blood Transfusion Service. In order to meet the increasing demands, 125,000 new donors must be found in 1954, making a total of 600,000 active donors. Copies of the booklet are obtainable on request at blood donor sessions.

# EFFECT OF LEUCOTOMY IN INITIATING NORMAL MENSTRUAL CYCLE AT AGE 36

BY

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Amenorrhoea is a feature common to all prolonged and debilitating illnesses, both physical and mental. However, it is customary to have a history of normal menstruation prior to the onset of the illness, and the amenorrhoea associated with the disease process is rarely absolute. It is unusual to find a patient who has never experienced a regular menstrual cycle developing a normal one in middle life after successful treatment of a prolonged nervous disorder. Such a case history is recorded below.

### Case Report

The patient was first seen in December, 1950, when aged 34. She complained of having been afraid to eat since the age of 14. She had a tendency to be constipated, and thought that if she ate a normal amount of food it would only accumulate within her body. Her family brought her up for medical advice, since they were concerned about her lack of appetite and consequent loss of weight. There was no relevant family history of physical or mental disorder. The patient's birth and early development were uneventful. She was, however, a shy and solitary child, and was excessively afraid of the dark. She was an inveterate nail-biter. From the age of 7 to 18 she was educated at a boarding-school, where she was a model pupil, but failed to take the school certificate. She became a student at the Royal College of Music and qualified A.R.C.M. With the outbreak of war she became a V.A.D., but lived at home to help look after an invalid mother. After the end of the war she continued to live at home, and became increasingly less able to look after her mother.

Menstruation began at 14. She had two brief menstrual flows, each lasting three days and separated by a period of two to three months. No further menstruation occurred until, at the age of 17, hormonal treatment produced two periods, and these ceased with the cessation of treatment. Thus, when first seen she had not menstruated for 17 years, and her previous menstrual history consisted of two scanty menses associated with the onset of puberty and two induced by hormones. She had always been an anxious, worrying person, preoccupied with her bowel function. She could not start her day's work until she had achieved a bowel movement. This often took a long time to carry out, and she had recourse to enemas and purges to allay her anxiety. Her manner had always been one of extreme politeness.

Her illness began with the onset of puberty at the age of 14. She had developed well, and weighed 9 st. 2 lb. (58 kg.). She felt rather self-conscious about her adolescent obesity, since she was the object of some teasing. At that time a fear of eating developed; she thought the food might fail to pass through her bowels, and she began to conceal the food she did not eat. She worried excessively about defaecation, and the sight of the lavatory book with its crosses haunted her. Her defaecation ritual was so prolonged that it interfered with her participation in normal morning school routine, and during the rest of the day her mind was preoccupied with ruminations on the subject of bowel function. She ate little, and gradually lost weight. Life at home made no great demands on her, but the weight loss continued. In 1947 she had remedial treatment in Ruthin Castle Hospital. This consisted of paraffin wax baths, which made her feel slightly better. In 1949 she entered a psychiatric hospital, but had no treatment apart from psychotherapy, and after three months she felt worse and discharged herself. Depression, fatigue, coldness, and inability to concentrate were her chief complaints. She became more anxious, had panic attacks, and slept badly, finding it difficult to get off to sleep. She was eating little, and her main meal consisted of two gooseberries and half a tomato.

On physical examination (December 12, 1950) she was seen to be grossly emaciated, and looked like a Belsen survivor (Fig. 1). She weighed only 5 st. 4 lb. (33.6 kg.). No other physical abnormality was noted, apart from acrocyanosis of the extremities. Her blood pressure was 100/60 mm. Hg. There was no hirsuties of the anorexic type. She was extremely tense and anxious, and it was some time before she gained enough confidence to talk at length about her preoccupation with her bowels and her compulsion to starve herself. B.M.R. was −36; 17-ketosteroids, 3.6 mg. in 24 hours. Psychological testing showed her to be of normal intelligence, and the Rorschach test confirmed the presence of obsessive traits.

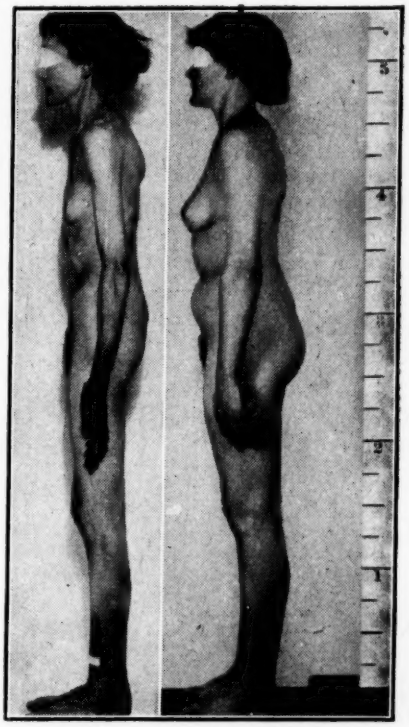

FIG. 1 FIG. 2

FIG. 1.—Photograph of patient in December, 1951. FIG. 2.—Photograph of patient in February, 1953.

After admission to hospital modified insulin treatment was given morning and afternoon. By February 18, 1951, her weight had increased to 7 st. 2 lb. (45.4 kg.), but her tension had increased also, and she required 3 to 5 gr. (0.2 to 0.32 g.) of sodium amylobarbitone to enable her to sleep through the night. It was difficult to persuade her to take enough food with the insulin. In turn, she frequently and anxiously requested enemata to rid her body of the accumulated food. With this small gain in weight, her tension reached unbearable limits, and it was decided that the only treatment likely to help her was a very modified leucotomy.

An anterior lower pole operation was therefore carried out on February 20 by Mr. Harvey Jackson. Recovery from the operation was uneventful, apart from the fact that she lost about a stone (6.4 kg.) during the week in which the operation took place. In the following week she regained that amount within five days, and it was apparent that modified insulin therapy played but little part in this gain in weight, so it was discontinued. She still continued to increase in weight without special treatment. No attempt was made to force her to eat. She still talked at great length about her defaecation difficulties, and made her customary demonstration against regular meals, but she was often discovered eating surreptitiously in the larder, and scraping the communal butter and jam dishes. She was no longer fastidious in her habits and polite in her manner. She told people precisely what she thought of them, and made no attempt to hide her true feelings. Her sleep was good, however, and nine days after the operation she had her first spontaneous bowel movement—that is, without purge or enema. Within three weeks of operation, normal bowel function was established, and her customary politeness of manner returned. She still found it difficult to eat

communally, but she continued to grow heavier. When discharged from hospital on April 25 her weight was 8 st. 4 lb. (52.6 kg.).

Subsequently she became a welfare worker with a charitable organization in London, and was able to lead an independent existence away from home. In July it was noted that her weight increased to 8 st. 13 lb. (56.7 kg.), almost her best weight. In the autumn of 1951 she took a course in domestic science, and early in 1952 became a cook in the Y.W.C.A. On June 25, 1952, menstruation began, the flow lasting for four days. She menstruated again on August 5 and September 4, and normal menstruation continued at intervals of approximately 28 days. When last examined (February 16, 1953), she looked well (Fig. 2), and her weight was 8 st. 11 lb. (55.8 kg.). Her blood pressure was 150/90 mm. Hg. Her bowels had remained regular without aperients, and she said, "When I look back and think what it was like before the operation, I can't get over it." She remains polite, and still retains some mild obsessive traits such as checking door locks and light switches. On March 9, 1953, the 17-ketosteroids were 8.2 mg. in 24 hours.

### Discussion

The most interesting feature of this history is that menstrual function did not begin immediately after the operation. Almost a year elapsed after the patient had reached her top weight before the flow began (Fig. 3). This point has been

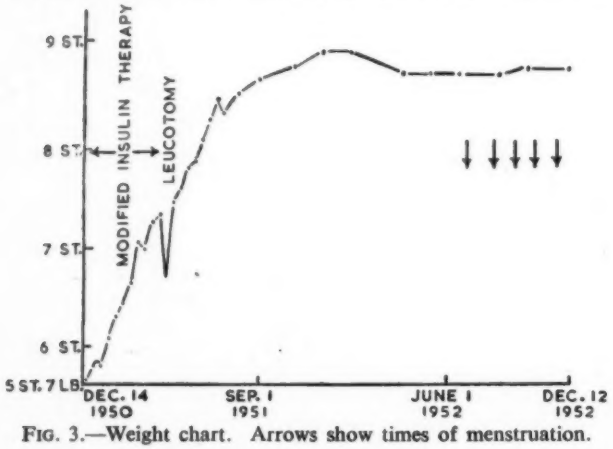


FIG. 3.—Weight chart. Arrows show times of menstruation.

commented on by Sargant (1951), who described two patients with prolonged amenorrhoea. They were also relieved to some extent by leucotomy, and the restoration of body weight was associated with the return of menstrual function. It was noted that in the obsessive patient a gain in weight aggravated tension, but in the leucotomized patient the normal body weight could be reached without excessive tension, and menstrual function could be established.

Hubble (1952) also considered that the restoration of menstrual function depended upon normal nutrition and absence of emotional stress.

### Summary

The history is given of a patient who began to menstruate normally for the first time at the age of 36. So far as is known, no patient similar to this has ever been described before. She was a woman of obsessive personality, who had kept her weight down by living on an inadequate diet for many years. The operation of prefrontal leucotomy relieved her tension and enabled her to gain over 3 st. (19 kg.) in weight fairly rapidly. Sixteen months after the operation, and almost a year after she had reached her best weight, menstrual function began. The point is made that regular menstruation depends upon a good level of nutrition, the maintenance of normal body weight, and the absence of excessive emotional tension.

ADDENDUM.—Since this paper was written, nine months ago, and while awaiting publication, further interesting observations have been made. Feeling so much better, the patient took on more arduous work as an assistant cook in a large restaurant. The strain of this caused her menstruation to cease for three months, but it returned when she went on holiday. At the moment she is doing a very difficult job, and her periods have been absent for the past two months. Because of the modified nature of the leucotomy she remains overconscientious and somewhat anxious. This provides further evidence that in such patients normal menstruation may depend both on restoration of physique and on freedom from undue tension. Her weight remains good.

My thanks are due to Dr. William Sargant for his kind interest in this paper.

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# Medical Memorandum

## A Case of Dracunculiasis (Guinea-worm) in Nairobi

An Indian carpenter aged 32 complained of a painful swelling between the last two digits of his left foot. He had noticed this lump for about a week, and it was growing steadily and becoming increasingly painful. He had had pain in the left knee and very intense pain in the left groin six weeks before. The swelling resembled an abscess which was not ready for lancing. There was considerable cellulitis around the swelling. I asked him to apply hot fomentations for a day or two. He came to me forty-eight hours later in a state of great agitation and excitement, because he saw, to his horror, what appeared to him to be a horrible snake coming out of his foot. I told him not to be alarmed, and that he was not to pull or in any way interfere with the worm, but that he should wind it gently and carefully round a stick. Also that he should not allow it, if possible, to come in contact with water. He preferred to pass a thread through it and then wind it round his toes as it is done in India.

[*Photo : Ram Singh*

The worm seemed to come out at the rate of about an inch a day, and the cellulitis and the swelling had disappeared in about a week. The whole worm was extruded in the course of 23 days. It was the typical *Dracunculus medinensis*, about 2 ft. (60 cm.) in length, and the thickness of a knitting needle. It was white in colour.

The patient stated that he went to India nine and a half months previously. He stayed in a village near Jamnagar, which, I believe, is an endemic area for dracunculiasis. While he was there he had heard of more than 200 cases in that area. In one case the whole worm was extruded in 24 hours. He stated that he had drunk well-water which had not been boiled.

The remarkable thing is that he did not show any of the usual clinical symptoms such as fever, diarrhoea, vomiting, and urticaria, which are associated with dracunculiasis at the time of the arrival of the worm to the surface for extrusion. He complained only of pain in the knee and the left groin.

Nairobi. AYRES L. RIBEIRO, M.R.C.S., L.R.C.P.

# Reviews

## TROPICAL DISEASES

*Clinical Tropical Diseases.* By A. R. D. Adams and B. G. Maegraith. (Pp. 508; 65 figures. £2.) Oxford: Blackwell Scientific Publications. 1953.

Provision in concise form of information necessary for the diagnosis and treatment of the commoner tropical diseases is something that several authors have attempted. There is no doubt of the need for such a volume, but in time most have expanded into large works of reference, too bulky to be the constant companion of the majority of practitioners in the Tropics. The authors of this book plan to supply the essential facts of diagnosis and treatment as dogmatically and as concisely as possible, to avoid giving information of an encyclopaedic nature, and to include only brief descriptions of organisms causing diseases, their identification, and the vectors carrying them. This plan has been well maintained throughout and is admirably suited to an easily transportable volume. Such a work fills a much-needed want and is a welcome addition to the literature. It is lucidly written, authoritative, up to date, and well illustrated. It must be counted among the best of its kind, and will undoubtedly and deservedly gain great popularity.

A. W. WOODRUFF.

## EMOTIONS AND THE SKIN

*Emotional Factors in Skin Disease: A Psychosomatic Medicine Monograph.* By Eric Wittkower, M.D., and Brian Russell. M.D. With forewords by Dr. R. M. B. MacKenna and Professor D. E. Cameron. (Pp. 214. £1 12s. 6d.) London: Cassell and Co. 1953.

It requires courage to write of the emotional factors in clinical medicine. The emphasis is so much more on the art than the science of practice in an age that is every moment becoming more highly scientific and is measured entirely by that yardstick. It is difficult to avoid the verbosity of the psychiatrist and his jargon, and the writer must constantly lay himself open to criticism it is not easy to refute and hold himself up to ridicule damaging to his reputation and trade. Drs. Wittkower and Brian Russell avoid these dangers and present their thesis in reasonable language, though some readers may regret that they use American spelling and, often, idiom.

They give a general review of the evolution of the psychosomatic approach, chapters on anatomy and physiology of the skin with special attention to nervous mechanisms, and instruction in the investigation and management of the patient suffering from skin disease. The main thesis of the work turns upon the conception that particular personality types and emotional configurations produce particular patterns of autonomic disturbance. Such disorders as pruritus ani, eczema, seborrhoea, psoriasis, and urticaria are analysed from this aspect. A number of patients suffering from each disease, often Army personnel, are compared with a control group as regards personality, childhood and adult situations, and the circumstances at the onset of the disease. The conclusions drawn have the suggestion of statistical support, but the evidence is not always convincing. There is an element of truth in the thesis propounded, though the authors are well aware that it is not the whole truth. Nevertheless this is a valuable contribution to dermatological literature, for there have previously been few attempts at a systematic approach to or a psychiatric appraisal of these difficult problems. Such literature as exists is briefly reviewed.

To many who would accept much of the truth which lies behind the psychosomatic approach some of the literature remains unattractive. It may be that too much attention is devoted to case details, intimacies that belong strictly to the consulting-room and should not escape beyond it. It would seem possible to dwell at greater length on the general principles and to a less extent on details.

J. T. INGRAM.

## VENEREAL DISEASES

*Progress in Venereology.* By R. R. Willcox, M.D. (Pp. 195; 36 figures. 21s.) London: William Heinemann. 1953.

A problem experienced by all scientific investigators, and by medical workers in particular, is the difficulty of ascertaining the facts already known about a given subject. Were all data readily available, progress would be greatly accelerated and many long and expensive investigations would never be started.

This book attempts to solve the difficulty for the venereologist and for those who write about venereal diseases, for it contains some 1,700 references covering the years 1946–1951. Probably no era has been so revolutionary in research or so dramatic in therapeutics as the immediate post-war years covered by this *index medicus* of venereology. It is not a manual for the student or general practitioner, nor is it a statement of the writer's personal opinions supported by references, for his own ideas have been rightly kept to a minimum. It is, however, a book of reference for workers in all branches of venereology, and a review, arranged coherently but hardly in narrative form, of the progress made during this comparatively short but productive period. The subjects include the tropical venereal diseases, experimental and animal syphilis, endemic syphilis, yaws, pinta, non-gonococcal urethritis, and venereal-disease control. Naturally the references on syphilis fill no less than half the volume, for a multiplicity of problems surround this disease, and even now the optimum therapeutic measures remain in doubt. The book includes sections on immunity; the microscopical, serological, and dermatological diagnostic tests; prenatal and congenital syphilis; and the treatment of all types of syphilis.

There are many excellent illustrations, graphs, and tables. The graphs depicting the decreasing incidence of venereal disease after the war are ingeniously superimposed, so that the trends in Great Britain can be compared with those in the United States. These trends agree in general. The fall in the incidence of early syphilis in the U.S.A. from its 1947 peak was 82.9% in four years, and in Britain was 87.1% within five years from its 1946 peak. Similar drops have occurred following previous wars, but the fall since the last war had been much more rapid chiefly owing to penicillin. This was also responsible for a similar decline in the incidence of fresh gonorrhoea in both countries. Exceptions are the cases of late syphilis, which increased in England and Wales from 4,000 in 1941 to 5,000 in 1951, while over the same period they decreased from 200,000 to 100,000 in the U.S.A. Similarly during the same years the deaths from aneurysm rose from 625 to 680 per annum in Britain, while they decreased from 3.0 to 2.5 per 100,000 of population in the U.S.A.

Under the section on immunity in animal syphilis, venereologists, and medical practitioners, too, will be interested to read the author's account of the "rebound phenomenon" following the withdrawal of cortisone in the treatment of rabbit syphilis, and the conclusion that this drug may be dangerous to give to human patients with cardiovascular syphilis. Moreover, the effect of cortisone on experimental syphilis in the rabbit is to cause a far more abundant multiplication of spirochaetes in the lesions and in the blood than in the controls. Furthermore, A.C.T.H. fails to inhibit or suppress the Herxheimer reaction induced by penicillin in the rabbit. These investigations were carried out by different groups of workers, none of whom could previously have suspected that some connexion exists between the action of cortisone, A.C.T.H., and hyaluronidase—the spreading factor which acts upon the ground substance to produce an environment favourable to the growth of spirochaetes. This is an example of the inestimable value of the correlation of knowledge in one volume.

Many British clinics are stated to have abandoned bismuth as well as arsenic in favour of penicillin alone in the treatment of early syphilis. This may be a risky procedure in seropositive cases, for during the past twelve months indications suggest an increase in the cases of late

syphilis. Some of these were treated for early syphilis with penicillin alone during the war. This danger may be avoided when the new diamine penicillin comes into more general use.

In the section on the treatment of gonorrhoea with penicillin the venereologist will be relieved by the information that "no enhancement factor" could be found in unrefined penicillins which could improve on the performance of crystalline penicillin G. Then he can enjoy contemplating the relative potencies of the various penicillin fractions G, F, X, and K. A few pages later he may feel apprehensive when he reads about penicillin failures and penicillin-fast strains of gonococci, until he cheerfully recalls that injections of hyaluronidase have been used successfully in provoking the appearance of the gonococcus when all other tests of cure have failed.

In general, a few sentences summarize each reference; these have been placed under their appropriate chapters and sectional headings, so that a five years' résumé can be obtained almost at a glance. This epitome of progress provides signposts to the laboratory investigator, is valuable to the therapeutist, and indispensable to the medical writer.

T. ANWYL-DAVIES.

## LOCAL ANALGESIA

*Conduction Anesthesia.* By George P. Pitkin, M.D., F.A.C.S., F.I.C.A. Second edition. (Pp. 1,005; 585 illustrations. £9.) Philadelphia and London: J. B. Lippincott Company. 1953.

This book gives the fruits of Dr. Pitkin's life's work together with additions on recent developments by other authorities. It includes accounts of local infiltration, nerve blocking, and combinations of them; single-injection and continuous spinal analgesia; caudal block; peridural block; and refrigeration analgesia. The two final chapters are on therapeutic nerve block and complications of conduction anaesthesia.

It is unfortunate that the opportunity has not been taken in this second edition to rectify certain defects; the work could be greatly improved by re-editing and condensation. It contains nearly six hundred illustrations, many of them of excellent quality, but most of those in the anatomical section are taken from Hirschfeld and have lost clarity in reproduction; poor labelling makes these difficult to follow. Pictures of the various techniques are, in general, well drawn, but are inadequately labelled, and often they are not well related to the accompanying text. Many of the diagrams are redundant and provide little essential information. The text is often disappointing in style and has been inflated by frequent repetition of elementary general principles. It does, however, give a fairly complete account of regional block procedures.

Despite these criticisms this is a useful reference book, but there is no doubt that most British anaesthetists will be deterred by the excessive price from adding it to their libraries.

C. F. SCURR.

## E.C.G. BOOKLET

*Introduction to the Interpretation of the Electrocardiogram.* By Louis N. Katz, M.D., R. Langendorf, M.D., and Alfred Pick, M.D. (Pp. 78; 61 plates. 19s.) Chicago: University of Chicago Press. London: Cambridge University Press. 1953.

This "booklet," as the authors call it, is hardly even an introduction to the subject. But one must allow that in the chapter on genesis of the electrocardiogram a fairly successful attempt is made to discuss this matter from the aspect of the vector. This is right enough, but unfortunately the treatment is so short that it is doubtful whether anyone who is entirely a beginner would understand it. The result is that there are rather wide gaps in the steps of reasoning, which make it difficult to follow. More of the really basic physiological facts are needed. The chapter on technique is clear enough, but that on the procedure in reading an electrocardiogram seems to come too soon. There follow sixty-one plates of various abnormal curves. There are some omissions of the rarer arrhythmias, but too few curves of those which show disease of the muscle. Each plate shows the three standard leads with some five or six complexes—only one complex is shown of each unipolar lead. It is surely redundant to show more than any one lead in illustrating an arrhythmia, and in the case of myocardial disease one complex alone is needed. Much economy in space might have been obtained and more abnormal curves shown had this been done.

The old bipolar standard leads receive far too much attention. Their relationship to the unipolar limb leads is not made clear. The illustration on p. 38 of ventricular tachycardia is poor; otherwise the plates are very good indeed. The diagnosis of bundle branch block, so easy from the precordial leads, is not made clear. The frequent use of that ambiguous word "involvement" causes obscurity, as does that of the word "strain." On p. 37 there is a mistake in the leads. Too little is said about the effect of the position of the heart. The examples of the curves of pericarditis seem hardly helpful.

Altogether this "booklet" is too old-fashioned. It does not attempt to provide a new approach to the subject which would simplify it and attract the student. All the old difficulties, nowadays so unnecessary, remain to balk him. There are numerous mistakes in the references in French, and some Latin words are wrong, too.

TERENCE EAST.

## CONSTITUTION OF BLOOD

*Blood Cells and Plasma Proteins: Their State in Nature.* Edited by James L. Tullis. Memoirs of the University Laboratory of Physical Chemistry related to Medicine and Public Health, Harvard University, No. 2. (Pp. 436. $8.50.) New York: Academic Press, Inc. 1953.

During the spring of 1951 a series of seminars was held at Harvard University to study problems of blood and blood transfusion, and they brought together speakers who were all experts in various aspects of these subjects. The chapters in the present volume, based on individual lectures given at the time but revised in the light of subsequent discussion, incorporate ideas put forward by all members of the group.

Dr. James Tullis has ably edited the book, which covers a wide range of subjects. After a historical prologue on the discovery of the formed and fluid parts of the blood, the characters and separation of plasma proteins are discussed by Edwin Cohn, from whose laboratory much fundamental work on protein chemistry has appeared. Section 2 comprises chapters on the blood-clotting mechanism in which coagulation factors and their interactions are discussed by Ferguson, Edsall, Surgenor, and Alexander, while Tullis sets out shortly his concepts of the physical nature of the blood platelets. Immunological problems are reviewed in four chapters in Section 3, while Sections 4 and 5 are devoted to the erythrocytes and leucocytes respectively. Section 6 is on plasma enzymes, their natures, characteristics, and measurement. Finally a section on lipo-proteins and protein–lipid relationships is given in five chapters, of which those by Oncley and Macheboeuf are the most notable.

The scope and interests in this book are wide and the contributors are well fitted to set out present knowledge in their respective fields. As with all rapidly developing sciences, however, it is almost impossible to be fully up to date with recent developments in a book of this nature; nevertheless, individual chapters are both stimulating and accurate, and Dr. Tullis is to be congratulated on its appearance.

A book of this scope can have only a limited distribution, since it is too advanced for the student, while for the specialist much of the material is available in more detail in journals. The price, too, will limit its sale. It would aid the international dissemination of scientific knowledge if the publication costs in the United States could be reduced, even at the expense of less excellent overall production.

H. PAYLING WRIGHT.

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## COMBINED PROPHYLACTICS

A recent report[1] from the World Health Organization on the production and testing of diphtheria and whooping-cough prophylactics gives much useful information, and in consequence inferior diphtheria prophylactics should not now be in use anywhere. Data on the quality of whooping-cough prophylactics are less satisfactory, mainly because there is no really suitable laboratory test by which to assess the protective efficiency of different preparations, but there is sufficient evidence to show that some vaccines confer considerable protection. Parents would welcome a specific prophylactic against such a common and debilitating infection as whooping-cough, but from the clinical aspect a troublesome problem arises: protection against whooping-cough is required some time earlier in the child's life than against diphtheria, since about two-thirds of the deaths from whooping-cough occur in the first year of life and in early childhood. Some of the difficulties in the way of a solution to this problem are discussed in our correspondence columns this week by Dr. Neville Butler.

At present a common procedure for prophylaxis against the two diseases is to give three inoculations of pertussis vaccine spaced at one-month intervals beginning at the age of about 4 months, followed by two doses of diphtheria prophylactic when the child is 9–12 months old. These five injections, and five clinic attendances, are a strain to both mother and child, so that the routine breaks down with increasing frequency, and it is the anti-diphtheria immunization which suffers most. The obvious way out of the difficulty is to give combined prophylactics. While this is administratively convenient, there are some technical difficulties. Moreover, some babies are born with significant amounts of maternally bestowed diphtheria antitoxin in their blood, and Barr, Glenny, and Randall[2] have shown that babies having 0.04 unit or more antitoxin per ml. of serum respond significantly less well to two spaced doses of A.P.T. than do those with lower concentrations of antitoxin. But this apparent disadvantage is of less importance than at first appeared, for Greenberg and Fleming[3] have shown that the differences disappear a year or more after inoculation. Again, objections that might be raised against the simultaneous immunization of very young infants are, first, that the proper development of antibody response might be impeded by mutual interference, and, secondly, that the child immunized so early in life is less well protected at the age of 5 years than one immunized at 9–15 months of age. As to the first objection, laboratory studies have shown that the mixture of pertussis vaccine with fluid diphtheria toxoid, far from depressing the response to diphtheria toxoid, significantly increases it.[4–8] It may be noted that the full immunization course is three spaced injections in a young infant, so that a baby weighing 14 lb. (6.4 kg.) and having 0.04 unit of antitoxin per ml. of serum would have all its circulating antitoxin fixed by a first dose of prophylactic containing 25 Lf or more of toxoid, thereby leaving the field clear for the two subsequent injections. Laboratory observations also indicate that the response to pertussis vaccine is little altered by the presence of the toxoid, adsorbed or fluid, as measured by the agglutination titre[4] or by mouse protection tests.[6] In extensive field trials of vaccines which conferred protection against whooping-cough Pearl Kendrick found that the addition of alum-precipitated diphtheria toxoid did not result in any less protection by the pertussis vaccine.[9 10]

As to the response of very young infants to immunization, Bell[5] reported that children who received two doses of a mixed product before they were 6 months old had fewer failures so far as diphtheria was concerned than children receiving the ordinary unmixed product at any age from 2 to 23 months. Nearer home, Bousfield[8] has recently shown that three spaced doses of combined prophylactic (fluid purified toxoid, with pertussis vaccine) administered to 182 infants 2–5 months old yielded a 100% Schick-negative reaction rate when the children were tested at the age of 15 months. With 1,170 older children, 6–24 months of age, the rate was 99.66% when measured three months after the third injection; while of 26 children about to enter school who had received one or two doses of P.T.A.P. (25 Lf each) with pertussis vaccine (10,000 million

1 *Wld Hlth Org. techn. Rep. Ser.*, 1953, No. 61.
2 *Lancet*, 1950, **1**, 6.
3 *Pediatrics*, 1950, **36**, 143; and 1951, **39**, 672.
4 Farago, F., and Pusztai, S., *Brit. J. exp. Path.*, 1949, **30**, 572.
5 Bell, J. A., *J. Amer. med. Ass.*, 1948, **137**, 1009.
6 Ungar, J., *Proc. roy. Soc. Med.*, 1952, **10**, 674.
7 —— *Irish J. med. Sci.*, 1952, p. 145.
8 Bousfield, G., address to the Royal Institute of Public Health, London, April 8, 1953.
9 Kendrick, P. L., *Amer. J. publ. Hlth*, 1942, **32**, 615.
10 —— *Amer. J. Hyg.*, 1943, **38**, 193.
11 *Brit. J. exp. Path.*, 1953, **34**, 12.
12 Barr, M., and Llewellyn-Jones, ibid., 1953, **34**, 233.
13 *British Medical Journal*, 1953, **1**, 504.
14 *Med. J. Aust.*, 1953, **1**, 800.

organisms per dose) at the age of 2–5 months, only one was Schick-positive. In 543 children who had received two doses of A.P.T. or P.T.A.P. at the age of one year the Schick test was found to be negative in 90.4%. Although the evidence relating to children immunized in very early life with combined prophylactic is not great in quantity, Bousfield's findings agree with those of Bell and clearly indicate that three doses of combined prophylactic in early infancy entail no increased risk of contracting diphtheria—which is indeed probably reduced—up to the age of 5 years, when the normal pre-school booster dose is given.

Two other observations affecting combined prophylaxis merit attention. Barr and Llewellyn-Jones[11] found that, in guinea-pigs which had been actively immunized against one antigen and subsequently received a combined mixture containing one component which was the same as previously used, the response to the second antigen, given as a primary stimulus, was significantly less than in normal control animals. In other words, primary responses are suppressed in the face of heterologous secondary responses. In practice this means that no child should receive a second or booster dose of one antigen at the same time as it is being given another for the first time. The other recently reported finding[12] is that when tetanus and diphtheria toxoids were mixed the responses to the two toxoids varied according to the ratio of the two components, excess tetanus toxoid resulting in a decreased response to the diphtheria toxoid without a significant gain in the anti-tetanus response. But when the balance of the antigens was optimal the responses to the tetanus component was greater than when that toxoid was administered separately. No doubt manufacturers of commercial preparations will take due note of this work.

The advisability of incorporating tetanus toxoid in other prophylactics administered early in life is another question which arises. In England tetanus is uncommon, but the fatality rate is high; and because of this much antitoxin is used prophylactically purely as a precautionary measure. On the other hand, some practitioners fear serum reactions so greatly as to be reluctant to use antitoxin. Conybeare and Logan[13] are strongly in favour of the active immunization against tetanus of children at pre-school age, but this, because of the reasons given above, should not be in the form of a combined prophylactic when the tetanus toxoid is being administered for the first time and the diphtheria toxoid as a booster. North and Patterson,[14] who carefully reviewed the evidence and paid due regard to the observations of Barr and Llewellyn-Jones on the mutual interaction of combined tetanus and diphtheria toxoids in antitoxin responses, prepared a combined prophylactic containing, per millilitre, 10 Lf of purified tetanus toxoid, 50 Lf of purified diphtheria toxoid, and 10 mg. of aluminium phosphate. They reported that two doses of 0.5 ml. (separated by six weeks) administered to infants between 6 and 18 months old resulted in very satisfactory protection against both diseases, with mean serum titres of 1.0 unit per ml. for diphtheria antitoxin and 1.6 units per ml. for tetanus antitoxin nineteen days after the second dose.

## TREATMENT OF CHRONIC BRONCHIAL INFECTIONS WITH ANTIBIOTICS

In both chronic bronchitis and bronchiectasis it seems likely that bacterial infection, while an important cause of symptoms, is essentially incidental. In chronic bronchitis the respiratory mucosa reacts abnormally, especially in the direction of excessive secretion, to a variety of stimuli; and this abnormality predisposes to bacterial infection, which, once established, modifies symptoms and may lead to secondary morbid anatomical changes. In bronchiectasis there is a structural rather than a functional abnormality of the bronchi, giving rise to symptoms as a result of bacterial infection but not returning to anatomical normality on abolition of such infection. The two types of abnormality of the bronchi—functional and anatomical—are of course often combined, though they may be seen separately.

This concept of the role of bacterial infection in these two types of bronchial abnormality receives support from the results of treatment with antibacterial agents. May,[1,2] investigating chronic bronchitis, found that potentially pathogenic bacteria were irregularly distributed in sputum specimens, while commensals, such as *Str. viridans*, nonhaemolytic streptococci, and *N. catarrhalis*, were more or less uniformly distributed. Pathogens, of which the most important were *H. influenzae* and pneumococci, were significantly related to pus in the sputum of chronic bronchitic patients. Treatment of the patients with appropriate antibiotics would cause the "pathogen" to disappear, together with visible pus, from the sputum. Pus and the "pathogen" reappeared at intervals varying from two days to eleven weeks after cessation of treatment. It is of great interest that some patients were more dyspnoeic after their sputum had been rendered mucoid, pre-

[1] *Lancet*, 1953, **2**, 534.
[2] Ibid., 1953, **2**, 899.
[3] Ibid., 1953, **2**, 903.
[4] *British Medical Journal*, 1953, **2**, 1067.

sumably because of the greater viscosity of the mucoid than of the purulent secretion. In only 1 patient out of 22 was the production of sputum completely suppressed for a time. Patients with only mucoid sputum generally gained no benefit from antibacterial treatment. Elmes, Knox, and Fletcher[3] investigated the effect of penicillin (given orally), chloramphenicol, aureomycin, and sulphadimidine in a small group of patients with chronic bronchitis. They found that all the antibiotics reduced the bacterial counts and the amount of pus in the sputum, but the clinical benefit was slight. Sulphadimidine had very little effect on the general bacterial flora, which is perhaps not surprising when pus is present. Penicillin reduced the total bacterial count, but tended to increase the numbers of *H. influenzae*, which remained the predominant organism for several weeks after the end of treatment. Chloramphenicol had its greatest effect on *H. influenzae*, which disappeared during treatment with this drug but reappeared in profusion two days after treatment was stopped. Aureomycin seemed to be less specific, producing a general reduction in the numbers of all bacterial types. A finding of topical interest was that in those patients with *H. influenzae* in the sputum there was a decided increase in the amount of pus in the sputum in foggy weather, whereas there was no such increase when this organism was not present. Elmes and his colleagues concluded that none of the drugs was suitable for prolonged administration as a prophylactic measure, partly because of side-effects, and partly because of the danger of encouraging the emergence of resistant strains of bacteria. Franklin and Garrod[4] have recently shown that chloramphenicol often had a most beneficial effect on the symptoms of bronchiectatic children, in whom the underlying abnormality —dilatation—was structural; in these children *H. influenzae* was present as a pure, or almost pure, infection. However, the remission produced by chloramphenicol proved to be transient; it was longer-lasting in the mild than in the severe cases. Unfortunately the toxic effect of chloramphenicol on the bone marrow, which led to the death of one of Franklin and Garrod's patients, makes it impossible to recommend the use of this drug over a prolonged period, and indeed raises doubts about the wisdom of using it even as short-term treatment except for severe infections not amenable to any other antibacterial agent.

In the management of these chronic bronchial infections, what is required to combat infection is a drug which not only will eliminate pathogenic bacteria already present but also can be given safely over a long period prophylactically. The object of such prophylactic treatment would be to stop or greatly reduce the incidence of the febrile exacerbations of purulent bronchitis and bronchopneumonia which tend to occur in these patients in the winter months. As Elmes, Knox, and Fletcher remark, such a drug should be cheap, free from toxic effects, effective against the whole range of bacteria found in chronic bronchial infections, and not likely to give rise to acquired bacterial resistance. Even if such a paragon among drugs eventually becomes available, the physician responsible for the care of a bronchiectatic child will still hope to find that the dilatation is confined to a part, or parts, of the lung which it is feasible to remove surgically: and in chronic bronchitis it is already clear that the elimination of bacterial infection will not always, perhaps not even very often, lead to more than slight and transient relief of the chronic symptoms.

## VIRUSES IN MEDICINE

As the momentum of scientific progress increases, so does keeping abreast of current thought and development become more difficult. Periodic reviews such as appear in the *British Medical Bulletin* fulfil a most useful role in presenting balanced and up-to-date accounts on a wide variety of subjects of general interest in medicine. It is perhaps salutary, on turning the pages of the current number of this *Bulletin*, entitled "Viruses in Medicine," to recall that Edward Jenner made his contribution to preventive medicine just a hundred years before viruses were first recognized as distinct from bacteria, and before even the start of the microbiological era of infectious disease.

Viruses are obligate intracellular parasites. Recognition of this fundamental characteristic took time and was not readily accepted. As Andrewes indicates in an introductory chapter, progress in the early days was not particularly rapid, but it allowed time for the development of sound laboratory technique largely concerned with overcoming the awkward requirement of cultivating viruses in living tissue; we are now beginning to reap the rewards of this pioneer work. Symptomatic infection in viral disease is often considered, not unnaturally, as all-important. But, as Sir Macfarlane Burnet emphasizes in writing on the ecology of these diseases, a much wider appreciation of the behaviour of viruses in nature is needed, certainly if we are to overcome the many difficulties in their control. Basically the questions in human viral diseases to which we want to know the answers in detail are, first, the processes that occur from the time that a virus first comes into contact with susceptible cells until such time as it is eliminated; and, secondly, what happens to viruses in the interval between epidemics when all appears to be quiescent. Working out the pathogenesis of viral diseases is not unlike doing a jigsaw puzzle of which some of the pieces cannot be found when they are needed. Smallpox is a case in point, and Downie

and Macdonald illustrate how some of the missing pieces in the pathogenesis of this disease are being found by combined observations on the natural disease in man and on the closely related infection of mice—ectromelia, or mouse-pox.

Until recently poliomyelitis was regarded as a strictly neurotropic infection with the emphasis on the central nervous system. In cases of paralytic poliomyelitis this is understandable, but first the virus has to reach the nervous system and often the infective process is halted before it is reached. Rhodes shows what a striking change has taken place in our outlook in the last few years. A short, early viraemic phase now seems to be clearly established as an essential part of the disease and as a precursor of C.N.S. involvement. Immunization methods are now being developed with the object of stimulating antibody production to prevent extension to the central nervous system, and the work on tissue cultivation of these viruses being carried out in the United States is distinctly encouraging. Recovery from viral infections is closely associated with the development of immunity, upon which fact is based the serological diagnosis of disease; and, as Wilson Smith stresses, the principles of viral immunology are perfectly straightforward in so far as they apply to circulating antibody. Indeed, there are excellent models in viral diseases for teaching the pathology of infectious disease.

Similar but more sensitive methods can be used to elucidate some of the epidemiological mysteries of viral diseases, and Isaacs shows how they are being applied to the study of influenza. The continually changing serological pattern of influenza A viruses in the last twenty years helps to explain how influenza manages to keep going in a population which has already experienced the disease.

Despite all this progress there remains a formidable list of viruses for which no susceptible host has yet been found other than man, and the inoculation of human volunteers, apart from other considerations, cannot be regarded as convenient. Hepatitis is one of the most important in this group, and, as MacCallum points out, work is restricted by our inability to cultivate the infective agents. The tissue culture method may well provide the answer here. It has undoubtedly revolutionized the outlook in poliomyelitis, and, as Andrewes indicates, it may be helpful in studying the common cold virus.

In contrast to bacterial and protozoal infections the treatment of viral diseases has been singularly unsuccessful. Apart from the rickettsiae and the larger viruses of the psittacosis group, viral diseases are uninfluenced by modern chemotherapeutic agents in current use. Nevertheless, as Weston Hurst points out, a variety of substances have been found which exert some effect on the growth of some of the smaller viruses in animal tissues, and so the outlook in this direction is not too bleak. Control of virus diseases by either preventive or therapeutic measures is likely to become more important in the next few years, and it is clear from reading this comprehensive account that in spite of what has been achieved much remains to be done. One thing is certain: this number of the *Bulletin* will undoubtedly arouse interest and act as a stimulus to further progress.

## DISSECTING ANEURYSM OF THE AORTA

Dissecting aneurysm of the aorta has in the past proved a difficult diagnosis, since the clinical picture may closely resemble that of other diseases. When the dissection lies in the thorax, the differential diagnosis includes myocardial infarction, cerebral embolus, pulmonary infarction, and thrombosis or embolism of a peripheral artery. In dissections of the abdominal aorta, nephrolithiasis, appendicitis, pancreatitis, ruptured viscus, strangulated hernia, and mesenteric embolus may be simulated. A second factor which tends to cause the diagnosis to be overlooked is that dissecting aortic aneurysm is not a very common disease. Since many cases die suddenly, the incidence of the disease is greater in coroners' than in hospital necropsies.[1]

Lodwick[2] describes two main types of dissecting aneurysm of the aorta—those due to degeneration of the media and those associated with atherosclerosis. An aneurysm of the first type usually starts in the thoracic aorta, with extension sometimes into the abdominal aorta and its branches, and is met with not only in older age groups but also in young adults. The aneurysm associated with atherosclerosis is commonest in the abdominal aorta and is seen in older patients. The presenting symptom is commonly pain. The site of the pain is related to the site of the dissection. It may be substernal, it may radiate to the back, or it may be greatest in the epigastrium, neck, abdomen, or lumbar region. In some cases there is a single acute attack of pain. In others, pain may be mild or even absent, and MacCuish[3] emphasizes the difficulties of arriving at a correct diagnosis then. Another method of presentation is sudden loss of consciousness accompanied by a profound fall in blood pressure. Sometimes there is a history of extra exertion or strain which immediately preceded the dissection.

The physical signs in those who survive the initial attack may be of two kinds. First, there may be evidence of occlusion or partial occlusion of any of the aortic branches. The coronary ostia may be partially occluded, with resultant myocardial ischaemia. Pulsation in a carotid or subclavian artery may be diminished and impairment of the cerebral blood supply cause visual disturbances or unconsciousness. Occlusion of the intercostal arteries may give rise to ischaemia of the spinal cord and hence to varied and transient neurological symptoms. With involvement of the branches of the coeliac axis, the clinical picture is one of an acute abdominal emergency. Haematuria may occur when there is occlusion of a renal artery, or anuria if there is complete occlusion of both arteries. Secondly, there may be evidence of rupture of the aneurysm, with

[1] Mote, C. D., and Carr, J. L., *Amer. Heart J.*, 1942, **24**, 69.
[2] Lodwick, G. S., *Amer. J. Roentgenol.*, 1953, **69**, 907.
[3] MacCuish, R. K., *British Medical Journal*, 1953, **1**, 71.
[4] Betts, J. W., and Rowlands, B. C., *ibid.*, 1953, **1**, 73.
[5] Oram, S., and Holt, M. C., *Brit. Heart J.*, 1950, **12**, 10.

haemorrhage. The blood may enter, according to the site of rupture, the pericardium, the heart itself, the mediastinum, the oesophagus, or the pleural or peritoneal cavities. When it enters the retroperitoneal space, it may sometimes track down through the inguinal canal and simulate a strangulated inguinal hernia.[4]

Radiology can be a helpful confirmatory test, particularly when the thoracic aorta is the site of dissection; when the site is in the abdomen, it is more difficult to delineate the aorta clearly. Lodwick[2] emphasizes the importance of serial films, which enable increase in size of the aorta to be recognized. Calcification of the intima, when present, may considerably help in assessing the thickness of the aortic wall. If this is found, on measurement, to be greater than 1 cm., a dissecting haematoma is almost certainly present. The electrocardiogram may give evidence of myocardial ischaemia in cases in which the coronary ostia or the coronary arteries themselves are involved in the dissection, or in which there has been a massive haemorrhage from rupture of the aneurysm. Oram and Holt[5] stress the transient and often rapidly changing nature of the ST- and T-wave abnormalities in serial electrocardiograms and also the rarity of Q waves. They suggest that these points may prove helpful in the differential diagnosis of such cases from myocardial infarction due to coronary thrombosis.

## EIRE'S MEDICAL SCHOOLS

Three months ago the five medical schools of Eire were visited by representatives of the Association of American Medical Colleges and of the Council on Medical Education and Hospitals of the American Medical Association. The publication of the "general report" of the American inspectors in the current issue of the *Journal of the Irish Medical Association* will do much to clear up misconceptions about the purpose of their visit and entirely dispel some quite unwarranted assumptions that their views about the Irish medical schools were largely unfavourable. In fact, as can be seen from the extract of the report in this week's *Supplement* (p. 228), the visitors found much to praise in the system of medical education in Eire, and also, as was to be expected, many differences from the American system. It is these differences in method, not differences in the quality of the final product turned out by the medical schools of Eire and the U.S.A., which have delayed and still delay the inclusion of the Irish medical schools in the international list which the two American organizations have been compiling. The report emphasizes that education in both the medical schools and teaching hospitals is in a state of transition at the present time. Changes are being made in the clinical training of the fourth- and fifth-year students, and the visitors examined somewhat critically the system by which the organization and conduct of teaching in the hospitals is the responsibility of the hospitals rather than of the medical school faculties. The report goes on to say that "in the United States experience has been such as to create a strong conviction that the interests of sound medical education are well served when the medical school is in a position to guide the entire educational programme of its students, both clinical and preclinical."

The American visitors were as well aware as their Irish hosts that the medical schools in Eire are not training doctors to practise in the U.S.A. Whether the report will have the effect of stimulating attempts to conform to American methods remains to be seen. Meanwhile Irish graduates will no doubt take in good part the mild criticism expressed in the report, will support efforts to overcome obvious deficiencies, and be gratified by the report's sincere tribute to the great tradition of teaching in Eire and to "the high ideals of the physician–patient relationship to which the Irish medical profession is devoted."

## POISONING BY TEETHING POWDERS

Paediatricians in many countries have reported evidence[1–18] that mercury administered to infants and young children may result in serious illness and may even cause or contribute to their death. We report at p. 1330 this week an inquest on a baby aged 10 months dying in Stoke-on-Trent of pink disease, after having been given over a long period teething powders containing mercury, and such reports as this again raise the question whether preparations containing mercury should be sold to the public without a doctor's prescription. Unfortunately the giving of teething powders is a tradition that dies hard, and indeed is often carried out simply because teething is expected, without the baby showing any discomfort or distress. As a result mercury may be given continually over long periods, with proportionate risks of mercury intoxication. Many paediatricians accept mercury as an important factor in the causation of pink disease, and there is evidence that mercury given in the form of teething powders can have a disastrous effect on the kidneys.[17] Only last week two fatal cases were described[19] of infants given such powders; both of them showed symptoms of pink disease and one evidence of severe renal damage.

The administration of calomel or grey powder to infants was accepted medical practice in the past, but the use of mercury by mouth in any form has no place in modern paediatric practice. Some varieties of teething powders do not contain mercury, and are therefore free of its dangers. By eliminating mercury from teething powders this potential threat to children would be effectively removed.


1 Baumann, T., *Schweiz. med. Wschr.*, 1949, **79**, 725, 750.
2 *Sixth Intern. Cong. Pediat.*, Summaries of Communications and Discussions, p. 213, 1950.
3 Bivings, L., and Lewis, G., *J. Pediat.*, 1948, **32**, 63.
4 Debré, R., *Arch. franç. Pédiat.*, 1952, **9**, 443.
5 Denys, P., *Acta paediat. belg.*, 1950, **4**, 16.
6 Fanconi, G., and Botsztejn, A., *Helvet. paediat. Acta*, 1948, **3**, 264.
7 —— *et al.*, ibid., 1947, **2**, supp. 4, 3.
8 —— and Morf, H., *Praxis*, 1949, **38**, 903.
9 Fischer, A. E., and Hodes, H. L., *J. Pediat.*, 1952, **40**, 143.
10 Holzel, A., and James, T., *Lancet*, 1952, **1**, 441.
11 Kirk, T. R., *J. Mich. med. Soc.*, 1951, **50**, 739, 744.
12 Van Creveld, S., and Paulssen, M. M. P., *Acta paediat.*, 1949, **38**, 82.
13 *Sixth Intern. Cong. Pediat.*, Summaries of Communications and Discussions, p. 212, 1950.
14 Warkany, J., and Hubbard, D. M., *Amer. J. Dis. Child.*, 1951, **81**, 335.
15 —— ibid., 1950, **79**, 388.
16 —— *Lancet*, 1948, **1**, 829.
17 Wilson, V. K., *et al.*, *British Medical Journal*, 1952, **1**, 358.
18 Baumann, T., *Schweiz. med. Wschr.*, 1952, **82**, 375.
19 Farquhar, H. G., *Lancet*, 1953, **2**, 1186.

# *CLINICAL PATHOLOGY IN GENERAL PRACTICE*

## TESTS OF RENAL FUNCTION

BY

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Assessment of renal function begins with an appraisal of the patient's past and present history, particularly in respect of oliguria, polyuria, nocturia, haematuria, and oedema; continues with the physical examination and urine analysis; and ends with special tests designed to provide information from which the extent and severity of the renal damage can be judged and the prognosis made. It is perhaps unfortunate that the term "renal-function tests" has come to be restricted to certain biochemical investigations of renal activity, because in practice much can be learnt about renal function from simple clinical observation and urine analysis. For example, the development of oedema, which may be insufficient to cause pitting of the skin at the ankles or over the sacrum and yet enough to cause a sudden increase in body weight, indicates impairment of at least one aspect of renal function—the ability to eliminate excess sodium.

The function of the kidneys is to maintain the volume and the concentration of the various constituents of the body fluids within narrow limits. To achieve this constant *milieu intérieur* the kidneys regulate the urinary excretion of water, sodium, chloride, and potassium; eliminate from the body the waste products of metabolism, such as urea; and maintain the acid-base balance by disposing of the acid substances usually present in a normal diet. Because the kidneys have so many functions, no single biochemical investigation will test all aspects of renal activity. Many tests have been evolved, and in recent years great progress in the understanding of renal physiology in health and disease has been achieved by investigations, too complicated for ordinary use, which measure the volume of fluid filtered through the glomeruli per minute and the volume of blood flowing through the kidneys per minute.* In this article only three tests of renal function—the water-concentration test, the blood urea, and the urea clearance—will be discussed. These have been chosen because they are simple, easily carried out, and within the scope of any laboratory.

### Indications

Tests of renal function may be helpful in answering any of the following questions. Is renal disease present in this patient who gives a history suggesting previous renal disease but in whom nothing or little abnormal is found on physical examination and urine analysis? What is the extent and severity of the renal damage in this patient who clearly has renal disease, and what is the prognosis? What measures can be taken in this patient with renal failure to ease the load on the kidneys? Only the first and second of these questions are considered, the last being a matter of therapeutics.

The value of renal-function tests as an adjunct to diagnosis is limited because the kidneys have considerable powers of reserve; although large amounts of renal tissue may be destroyed or removed, the remainder will continue to serve the functions of the body satisfactorily provided an excessive strain is not imposed. Tests of renal function are designed to provide such a strain, but even then extensive bilateral damage must be present before the tests show any abnormality, and by this time there are often protein and casts in the urine to indicate kidney disease. Nevertheless positive evidence of renal damage in some patients with glomerulo-nephritis in a quiescent phase, prostatic hypertrophy, bilateral pyelonephritis with sterile urine, and polycystic disease of the kidneys may not be obtained until tests of renal function are applied. In cases of unilateral disease, such as calculi and tumours, intravenous pyelography is a more useful adjunct to diagnosis.

In assessing the extent and severity of renal damage, and in making the prognosis, tests of renal function are of value when there is bilateral involvement and when applied at a suitable time in the course of the disease. For example, there is little indication for renal-function tests in acute glomerulo-nephritis when the patient's general condition and the degree of oedema, hypertension, proteinuria, haematuria, and oliguria are all indicative of the severity of the renal damage at the time. But when the acute phase is passed tests of renal function may indicate the extent of the residual damage. In those unfortunate patients in whom the disease proceeds to the chronic form, renal-function tests repeated at intervals are helpful in judging the tempo of progression.

### Water-concentration Test

This test has much to recommend it, because, apart from a urinometer costing about three shillings, no special apparatus is required, and the test can be carried out in a few seconds in the patient's home or in the surgery. Although a more sensitive index of renal damage than the urea-clearance test, the water-concentration test is a qualitative rather than a quantitative index of renal function, and does not measure the extent of renal damage or distinguish between moderate and severe degrees.

*Physiological Basis.*—The kidneys are made up of nephrons, each comprising a glomerulus, its tubule, and the accompanying blood supply. The glomerulus acts as a filter, and as blood flows through the glomerular capillaries fluid of the same composition as protein-free plasma enters the tubular lumen. As this filtrate passes down the tubule some 98 to 99% of the water and lesser amounts of the substances dissolved in it (so-called solutes such as sodium, chloride, and urea) are reabsorbed by the tubular epithelium and passed back into the blood stream. Because relatively more water than solutes is reabsorbed, the fluid contains at the end of the tubule more sodium, chloride, and urea per ml. of water than it did at the beginning. As the concentration of solutes increases, the osmotic pressure of the tubular fluid also increases, and this resists the further reabsorption of water. Thus to excrete a concentrated urine (and therefore a urine of high specific gravity) the tubular epithelium has to work against the osmotic pressure exerted by the tubular fluid. If the tubular cells are damaged the ability to reabsorb water will be impaired and the specific gravity achieved will be lower than normal.

*Technique.*—If a casual specimen of urine, free of protein and sugar, has a specific gravity of 1025 or more, renal function is probably normal, although, of course, renal

*The normal glomerular filtration rate is 100 to 120 ml. per minute; the normal renal blood flow is 1,000 to 1,300 ml. per minute.

disease may be present. If the casual specimen has a specific gravity of less than 1025, a water-concentration test should be carried out. The patient is asked to drink nothing after tea on the day before the test and to have a dry evening meal. The bladder is emptied on retiring and any urine passed during the night discarded. The following morning breakfast and all fluids are omitted, and the bladder is emptied at 8, 9, and 10 a.m. into separate jars. If the volume is too small to measure the specific gravity in the ordinary way, the volume of each specimen is measured and the urine diluted with one or two equal volumes of distilled water. The specific gravity is then measured and the last two figures of the observed value multiplied by two or three respectively to obtain the correct value for the undiluted urine.* Alternatively, a specially small urinometer is available for measuring the specific gravity of small volumes.

*Interpretation.*—If renal function is normal the specific gravity of at least one of the specimens voided at 8, 9, and 10 a.m. will be greater than 1025. In the elderly the concentrating power of the kidneys is somewhat reduced and a value of 1020 must be regarded as normal. A specific gravity of less than 1020 is evidence of renal damage; in severe cases it may become fixed at 1010 or 1012. A false result may sometimes be obtained if the patient has congestive cardiac failure, because excretion of oedema fluid during the night will simulate inability to concentrate. Failure to excrete urine with a specific gravity higher than 1003 to 1005 is found in diabetes insipidus.

### Blood Urea

*Physiological Basis.*—Urea is formed from the breakdown of proteins, and the level in the blood is largely governed by the rate of excretion by the kidneys. The concentration in the glomerular filtrate is the same as that in the plasma, and as the fluid passes down the tubular lumen some of the urea diffuses back across the epithelial lining into the blood stream, but the amount excreted depends largely upon the amount of fluid filtered through the glomeruli. Hence the concentration in the blood is influenced by the glomerular filtration rate, which depends upon the number of functioning glomeruli and the pressure and volume of the blood flowing through them, and by the rate of urea formation in the body, which depends chiefly upon the protein intake.

*Sample Required.*—About 5 ml. of venous blood is collected in a clean tube containing a small pinch of potassium oxalate powder. If the specimen has to be sent to the laboratory by post a few drops of formalin should be added.

*Interpretation.*—Normally the blood-urea concentration varies from 20 to 40 mg. per 100 ml., but values up to 50 mg. cannot be regarded as abnormal in the elderly. Since the urea level is influenced both by diseases of the kidney and by conditions in which the kidneys are not primarily involved, the causes of urea retention are conveniently considered under two main headings—renal and extrarenal.

### Renal Causes of Urea Retention

The degree of renal damage that must be present before there is urea retention depends to some extent upon the amount of protein in the diet. On an average intake adequate elimination of urea can be effected by as little as two-thirds of one kidney; therefore widespread bilateral kidney damage must be present before there is nitrogen retention of purely renal origin.

In acute glomerulo-nephritis the blood urea is often raised but rarely exceeds 100 mg. per 100 ml. In 90% of cases the symptoms and signs of the acute phase subside and the blood urea returns to normal, although in a small proportion proteinuria may persist and chronic glomerulo-nephritis develop many years later. Some 5% of patients die in the acute attack with severe oliguria and a blood urea that climbs progressively to levels of 300 to 400 mg. per 100 ml. In another 5% the disease is a little more protracted: these patients proceed over a year to eighteen months to progressive renal failure with a blood urea that rises steadily until the time of death. In the early stages of nephrotic nephritis, characterized by gross oedema, a normal blood pressure, and heavy proteinuria, the blood urea is normal, but if the condition progresses urea retention due to renal failure occurs in the later stages.

During the early phases of chronic glomerulo-nephritis there is no rise in the blood urea. The daily urine volume is normal and renal disease may be revealed only by proteinuria, casts, a raised blood pressure, or a poor water-concentration test. As the disease progresses more glomeruli become damaged. The glomerular filtration rate is decreased and less urea is filtered into the tubules. The blood-urea concentration therefore rises, but this automatically results in more urea being filtered, and despite the diminished glomerular filtration rate the same amount of urea is eliminated but at the price of a higher level in the blood. Thus a balance is struck, and a blood urea which rises from 30 to 100 mg. per 100 ml. and remains stationary at this abnormally high level is compatible with many years of happy and useful life, especially if the patient's blood pressure is normal. As the disease progresses more glomeruli are involved and the blood urea rises higher. The tempo with which the disease advances varies from patient to patient but is usually more rapid in those with hypertension. Estimations of the blood-urea concentration repeated at monthly or bimonthly intervals are helpful in deciding the speed of progression, and a urea level which rises in a month from 60 to 100 mg. and then to 120 mg. a month later usually indicates a worse prognosis than a level which remains stationary at 100 mg. per 100 ml.

The blood-urea level often remains within normal limits during the entire course of essential hypertension but may be raised during episodes of cardiac failure and in the malignant phase of the disease. A raised blood-urea level may occur in chronic infective, neoplastic, or polycystic renal disease and indicates bilateral involvement unless there are additional extrarenal causes of urea retention.

### Extrarenal Causes of Urea Retention

Any condition which reduces the volume or pressure of the blood flowing through the glomeruli may cause a rise in the blood-urea level, and this occurs in dehydration and shock due to severe and protracted vomiting, profuse diarrhoea, haemorrhage (particularly bleeding from a peptic ulcer), uncontrolled diabetes, and circulatory failure. In these pre-renal conditions which cause urea retention the raised blood level indicates a disturbance of renal circulation rather than intrinsic renal disease, and, provided the underlying cause can be corrected promptly, does not in itself signify a bad prognosis.

Any condition which obstructs the outflow of urine will cause back pressure on the kidneys and reduce the glomerular filtration rate. These post-renal causes of urea retention include prostatic hypertrophy, bilateral calculi, and carcinoma of the bladder. If the urinary obstruction can be relieved the blood urea returns rapidly to normal unless permanent renal damage has occurred.

### Urea-clearance Test

*Physiological Basis.*—The urea-clearance test is a measure of the renal efficiency in removing urea from the blood stream and excreting it into the urine: it is largely determined by the glomerular filtration rate. Normally the concentration of urea in the blood is about 20 mg. per 100 ml. and the amount excreted in the urine is about 20 mg. per minute. This quantity of urea would be provided if in one minute 100 ml. of blood passed through the kidneys

*If the urine contains enough glucose to give a yellow or orange precipitate with Benedict's solution, or enough protein to produce a thick precipitate on testing with sulphosalicylic acid, abnormally high specific gravities will result. With laboratory help a correction can be made by estimating the exact amount of sugar and/or protein present.

and each millilitre was completely cleared of its urea content. But the blood flowing through the kidneys is not completely cleared of urea and the blood-urea concentration in the renal veins is only slightly less than that in the renal arteries. Thus a clearance of 100 does not mean that 100 ml. of blood has passed through the kidneys and was completely cleared of urea, but that the amount of urea excreted in the urine in one minute is equal to the amount found in 100 ml. of blood. Efficient kidneys will "clear" a larger volume of blood per minute than diseased kidneys.

The rate of urea excretion is influenced by the urine volume. As the glomerular filtrate passes down the tubular lumen some of the urea diffuses back into the blood stream. When the rate of urine flow is slow, relatively more urea diffuses back than when the urine flow is fast. Allowances must be made for different rates of urine flow if the results of urea clearance are to be compared in different patients and in the same patient at different times. It has been found that when the urine output exceeds 2 ml. per minute the clearance of urea is maximal, and even if the urine output rises there is no further increase in the clearance of urea.*

*Procedure.*—The patient should eat an ordinary breakfast, and, although not essential, should remain in bed during the test. At about 9.30 a.m. he drinks a tumblerful of water: this ensures a high urine output and therefore maximal clearance, and also reduces the significance of any errors in measuring the amount of urine passed. The test begins at 10 a.m., when the patient empties his bladder and discards the urine. The bladder is emptied again at 11 a.m. and the urine saved. A sample of blood is taken about this time for estimation of the blood-urea level. At noon the bladder is emptied again and the urine saved. Urine need not be passed at intervals of exactly 60 minutes: provided the exact time is noted at which each specimen is voided the urinary output can be calculated in millilitres per minute. The volumes of the specimens passed at 11 a.m. and noon are measured, and a small amount (about 5 ml.) of each, together with the blood sample and a note of the urine volumes and exact times of voiding, are sent to the laboratory for determination of their urea content.

*Interpretation.*—The results are expressed as a percentage of the average clearance in normal subjects. Values of 75 to 100% or more are found in healthy children and adults, but may fall to 60% in the elderly. Values of 40 to 60% suggest mild impairment, 20 to 40% moderate impairment, and below 20% severe impairment of renal function. Diminished urea clearance is chiefly due to a decreased glomerular filtration rate, which may be caused by glomerular changes as well as extrarenal factors reducing the volume and pressure of blood flowing through the kidneys. When interpreting the results the relative importance of renal and extrarenal factors must be evaluated. In acute glomerulo-nephritis urea clearance is diminished but it is not until four to six months after the acute symptoms and signs have subsided that the urea clearance gives an indication of the extent of the residual renal damage. If after this interval the clearance is subnormal and shows no further improvement with time the outlook is poor, but the rate of progress of the disease is very variable from patient to patient. During the early stages of chronic glomerulo-nephritis urea clearance is often within normal limits, although the water-concentration test may be abnormal. Later, although the blood urea level may be within normal limits, urea clearance may be mildly impaired (50 to 60% of normal). With further deterioration the urea clearance is more reduced and associated with a raised blood-urea level, which in itself indicates diminished clearance. A temporary reduction of urea clearance may be due to superimposed hypertensive heart failure or salt deficiency, and thus the test should be repeated at intervals. In essential hypertension urea clearance is often normal for months or years, and then gradually decreases. In the malignant phase it is diminished at an early age.

*When the urine output is less than 2 ml. per minute the clearance diminishes in proportion to the square root of the urine flow. This is called the standard clearance in contrast to the maximum clearance.

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**Next article on Clinical Pathology.**—"Glycosuria and Hyperglycaemia," by Professor Charles H. Gray.

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## WELLCOME RESEARCH LIBRARY OPENED

### ROYAL SOCIETY OF MEDICINE EXTENSION

In the presence of a representative company of 300 people Lord Woolton on December 4 opened the extension of the library of the Royal Society of Medicine which is to be known as the Wellcome Research Library. An account of the library and of the events that led up to this enterprise appeared in the last issue (p. 1264). Lord Woolton deputized for Lord Salisbury, who was prevented by indisposition from performing the ceremony. The president of the Society (Sir Francis Walshe) was supported by Lord Webb-Johnson and by Sir Henry Dale (chairman of the Wellcome trustees). Those present included the chairman of the Wellcome Foundation (Mr. M. W. Perrin) and representatives of the Ministry of Health, the University of London, the Medical Research Council, the British Council, and the various medical societies.

Sir Francis Walshe thanked the Wellcome trustees most warmly for their generous gift of £125,000 which had made this venture possible, and spoke with gratitude also of the services of Sir Henry Dale, former president of the Society, whose interest in it had been long-standing and most practical.

Sir Henry Dale said that the Wimpole Street building was originally intended to have four stories, but financial stringency at the time of its construction, in 1911, caused those concerned to adopt a cautious policy and to build only three stories, with a flat roof and a strong enough foundation to support a fourth should this be necessary. After the second world war, with the influx of new Fellows and the great demand on the Society's facilities, there was a new urgency to the situation, and the Wellcome trustees were approached for help in the project for the fourth-floor extension. The trustees decided to offer £80,000 to the Royal Society of Medicine. The offer was accepted with gratitude, and a building committee was appointed. The work had been carried out at a time of steeply rising costs, and the Wellcome trustees finally increased their total benefaction to £125,000.

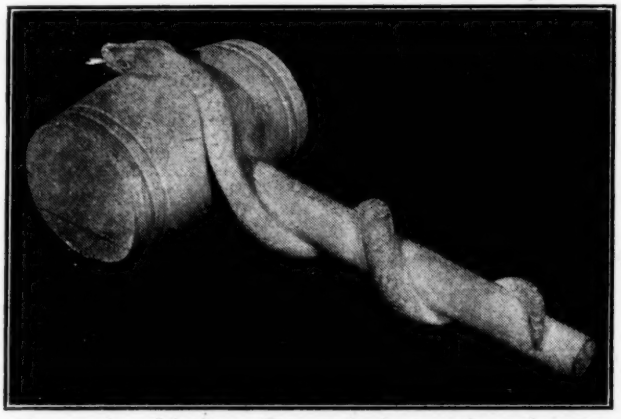
Lord Woolton said that he had several reasons for pleasure in performing the opening ceremony. One was his friendship for Lord Webb-Johnson; another his gratitude for the help he received from his medical advisers at the time he was Minister of Food; and a third and more personal reason was connected with his recent illness. "I owe so much to your profession. I owe to it the fact that I am here at all."

He had been told that the library contained a quarter of a million books. To house these was a gigantic task. The importance of the service of this library to medicine and medical research could not be exaggerated. He was told that it was the greatest medical library in Europe. It would remain the very proud possession of the present and succeeding generations of Fellows. In opening these beautiful rooms he congratulated the Society upon their possession, and the

Wellcome trustees upon the wisdom and public spirit they had shown in making this provision possible.

Lord Webb-Johnson expressed the thanks of the Society to Lord Woolton, and the company then adjourned for an inspection of the new extensions.

## COLLEGE OF GENERAL PRACTITIONERS' GAVEL



The gavel—made from the wood of an ancient plane tree from the Island of Cos—which the Greek Ambassador presented to the College of General Practitioners at their first annual meeting last month (see *Journal*, November 21, p. 1154).

## PAEDIATRICS IN U.S.S.R.

### VISIT OF RUSSIAN WOMEN DOCTORS

The Society for Cultural Relations with the U.S.S.R. arranged a meeting at their Kensington headquarters on November 30 on the subject of paediatrics in the U.S.S.R. The speakers were Dr. Ilina, chairman of the Executive Committee of the Medical Workers Union, and Dr. Kazantseva, professor of child health and director of the Paediatrics Institute of the Academy of Medical Sciences, Moscow. These two women doctors have spent a month in this country, visiting the children's hospitals and other institutions in ten cities. Both of them spoke in Russian and were interpreted.

Dr. Ilina spoke first of the concentration of health services, embracing the whole population, in the Russian State. All medical aid was free and accessible. Some 40,000 hospitals and other health institutions were destroyed during the war, but now all had been restored to pre-war level. Maternity and child welfare clinics numbered 7,500, and the paediatricians numbered 30,000. There were special faculties at the medical schools for the training of paediatricians, and at the secondary schools training facilities were available for nurses for children's hospitals.

#### The Paediatrician's Charge

In Moscow and Leningrad and other large cities a certain number of families were assigned to each paediatrician; a different standard applied in country districts. All children were allocated to clinics and each paediatrician was responsible for the children in a particular area. He looked after the child from birth until the age of 14. All confinements in towns took place in maternity homes. The local paediatrician in the place where the family lived was notified of a birth, and called at the home of the child within four days of the discharge from hospital. During the first year the child was brought to the clinic twelve times and during the second year from four to six times. The children's clinic, which looked after the child up to the age of 4, had on its staff specialists in tuberculosis and skin diseases, and, in the larger centres, in neurology. Two health visitors were attached to each clinic. Children over 4 attended a health centre. It was the rule that the same doctor cared for the child, well or ill. At hospital the child might come under the care of another doctor, but the local doctor was kept informed. All children, unless it was contraindicated, received B.C.G. at the maternity home, and the doctor at the children's clinic carried out immunization, which was compulsory, against diphtheria and smallpox. A full medical examination was made of all children when starting school, and as a rule a medical examination was carried out twice a year at the health centre. Mass radiography units were employed.

Dr. Ilina also described the postgraduate training of paediatricians. They were expected to attend courses after having spent three years in practice, and during their postgraduate training they received full salary and in addition a special maintenance grant. She surprised her audience by saying that the average working hours of the paediatrician were from 4½ to 6 a day. There was a large paediatric association with its headquarters in Moscow, and branches in the principal towns; also a research institute, which was part of the Academy of Medical Sciences, and a scientific council at the Ministry of Health which met periodically to determine scientific and organizational questions.

Dr. Kazantseva described some special studies on infants in the clinics. One study had been made of the conditioned reflexes. A month-old baby placed in a cot, above which a red bulb had been lighted on every occasion when the feeding bottle was used, would, when the bulb was lighted but the feeding bottle not applied, make sucking noises, showing that the cerebral cortex was already functioning. It had also been shown that a month-old baby could react to a particular sound which had become familiar to it, and turn its head to the source from which the sound came. Experiments had been made on the amount of sleep an infant required within the twenty-four hours, and the functioning of the cerebral cortex was found to depend considerably on the balance between wakefulness and sleeping. Should the baby be fed before or after sleeping? It had been shown that the gastric secretion was more active if a rest was taken before the feed. Indeed, they had coined the phrase, "Sleep before dinner is golden."

Other work described by Dr. Kazantseva was concerned with infant feeding, gastro-intestinal disturbance, and rheumatic fever.

The addresses were listened to appreciatively by a large audience, mostly of members of the medical profession.

## SUPPLEMENTARY LIST OF APPROVED NAMES

The General Medical Council has authorized the following "approved names" of drugs, selected by the British Pharmacopoeia Commission. The list supplements the consolidated list of names published in January (which included all the approved names issued since 1948) and the supplementary lists printed in the *Journal* of April 18 (p. 882) and August 1 (p. 273).

| *Approved Name* | *Other Names* |
|---|---|
| Amodiaquine | 7 - Chloro-4-(3-diethylaminoethyl-4-hydroxyanilino)quinoline. "Camoquin." |
| Azovan Blue | Tetrasodium salt of 4:4′-bis-[7-(1-amino-8-hydroxy-2:4-disulpho) naphthylazo]-3:3′-bitolyl. Evans Blue. |
| Carbomycin | An antibiotic produced by a strain of *Streptomyces halstedii*. "Magnamycin." |
| Laudexium Methylsulphate | Decamethylene - 1 : 10-bis-1-(3:4-dimethoxybenzyl)-1:2:3:4-tetrahydro - 6:7-dimethoxy-2-methyl-*iso*quinolinium methylsulphate. "Laudolissin." |
| Meclozine | 1-*p*-Chlorobenzhydryl-4-*m*-methyl - benzylpiperazine. "Ancolan" is the dihydrochloride. |

# Correspondence

## Desensitization to Streptomycin and P.A.S.

SIR,—The paper by Dr. John Crofton (*Journal*, November 7, p. 1014) was of considerable interest and import. There have been few reports in the literature of attempts at desensitization to streptomycin—a most valuable procedure if it can be carried out successfully. The best route, frequency, and dosage of desensitizing injections have not yet been worked out. That being so, it should be useful for those faced with this problem in the future to know of the varied experiences of others, and I would like to record the technique used with a nursing sister under my care who gave a history that she had developed oedema and peeling of the eyelids and of the flexures of the elbows in the autumn of 1947 after handling streptomycin. The rash cleared after avoidance of streptomycin, but recurred in the spring of 1948 after a short re-exposure in which she had only given two injections. In the spring of 1952 there was a further slight recurrence after giving a single injection, and another in November, 1952, after checking injections: this became worse after giving some injections.

On examination on December 19, 1952, there was peeling of the eyelids, the left more than the right. Patch-testing was performed with streptomycin 1/1,000,000, 1/100,000, 1/10,000, and 1/1,000, and all tests were negative except the 1/1,000 dilution, which at 70 hours showed slight redness and oedema. The left eye had become swollen about 60 hours after the application of the patch. On re-examination five days after the application there was still marked pinkness and papulation at the 1/1,000 site, but the other test sites were negative. Both eyelids had, however, recently been oedematous and pink. In view of the possibility of some other cause, such as plants, having an influence, patch-testing was also performed to chrysanthemums, with negative results. On September 25, 1953, an intradermal injection of 0.1 mg. of streptomycin was given and on the next day an injection of 0.2 mg. On September 27 erythema and oedema 1 cm. in diameter were noted at the site of the first injection, and this reaction had become more marked after receipt of the second injection. At the site of the second injection there was only a minor response. The eyelids had become sore six hours after the second injection, but this soreness subsided in 24 hours.

Subsequent injections were as follows:

| Date | Amount (mg.) | Result |
|---|---|---|
| Sept. 28 | 0·1 | |
| „ 30 | 0·2 | No reaction to previous injection |
| Oct. 2 | 0·3 | „ „ „ „ „ |
| „ 4 | 0·3 | Soreness above eyes and old sites flared up |
| „ 8 | 0·4 | No reaction to previous injection |
| „ 9 | 0·5 | „ „ „ „ „ |
| „ 11 | 0·5 | Slight „ „ „ „ |
| „ 12 | 0·6 | No „ „ „ „ |
| „ 13 | 0·6 | Slight „ „ „ „ |
| „ 14 | 0·7 | No „ „ „ „ |
| „ 15 | 0·8 | „ „ „ „ „ |
| „ 16 | 0·9 | „ „ „ „ „ |
| „ 17 | 1·1 | „ „ „ „ „ |
| „ 18 | 1·4 | „ „ „ „ „ |
| „ 19 | 1·5 | „ „ „ „ „ |
| „ 20 | 1·6 | „ „ „ „ „ |
| „ 21 | 1·7 | „ „ „ „ „ |
| „ 22 | 1·9 | „ „ „ „ „ |
| „ 23 | 2·2 | „ „ „ „ „ |

There was no reaction to this last dose, and the patient was advised deliberately to expose herself to streptomycin, first by checking doses, and secondly by giving injections. She checked two injections without upset and then filled a syringe with streptomycin. Seven hours later there was some moistness and itching of the eyelids, but this subsided rapidly and in her opinion was only half as bad as before. Subsequent further checking caused no reactions.

November 9 Patch test with 1/1,000 streptomycin
„ 11 Above patch negative: 1/500 applied
„ 13 Above patches negative: 1/250 applied
„ 16 All above patches negative: 1/100 applied
„ 18 All patch areas negative

The patient had meanwhile been checking and giving injections, and 21 hours previously had deliberately spilled some streptomycin on her fingers and let it dry on, washing her hands three-quarters of an hour later. There had been no reaction although there previously would have been under these circumstances at six hours; but on the evening of November 18 there was slight swelling of the eyelids which subsided by next morning. On November 19 the 1/100 patch became red and slightly swollen. This reaction faded within 24 hours.

It would appear that this course of intradermal injections has diminished the patient's sensitivity tenfold, a positive reaction being obtained now with a dilution of 1/100, comparable in intensity to that previously obtained with a dilution of 1/1,000. It remains to be seen whether desensitization by this technique is permanent or whether periods of non-exposure to streptomycin, as, for example, on holiday, will be followed by an increase of sensitivity. Our knowledge of the mechanism of eczematous sensitization is most incomplete, and Seeberg's work[1] suggests that the reticulo-endothelial system and the lymph nodes play an important part in the formation of antibodies. There are reasons for believing that the dermis also plays a significant part in immunological processes.

In this patient a partial immunity has been obtained by doses of up to 2.2 mg. by the intradermal route, whereas Crofton used doses up to 1 g. by the intramuscular route. It would be of practical value if we could establish with some degree of certainty whether there is any advantage in giving injections intradermally rather than by the subcutaneous or intramuscular route, when attempting desensitization.—I am, etc.,

BRIAN RUSSELL.

London, W.1.

REFERENCE

[1] *Acta derm.-venereol. (Stockh.)*, 1951, **31**, 592.

## A Cosmetic Amputation

SIR,—As a member of one of the appeal tribunals under the Ministry of National Insurance, I am frequently confronted with the unfortunate results of an operation still recommended in many textbooks—the removal of the index or little finger with part of the metacarpal.

The operation is recommended as being more cosmetic. It may for this reason have some place in the treatment of patients whose livelihood depends on the appearance rather than the usefulness of their hands. Even in them it postpones rather than prevents the recognition of the mutilation. It is a bad operation in working men and women. The scar is more apt to remain tender and to develop neuromata than that of a disarticulation at the metacarpo-phalangeal joint. The deep scar nearly always limits slightly the movements of the adjoining finger. The loss of 25% of the breadth of the palm is a most serious disability to any manual worker. From the point of view of insurance, this operation usually steps up the pensionable disability in the case of the little finger from 7% to 12% or 15%, and in the case of the index finger from 14% to 20%.—I am, etc.,

HENEAGE OGILVIE.

London, N.W.8.

## Early Immunization

SIR,—The whooping-cough mortality in England and Wales under the age of 6 months in 1950 was 180[1] or 45% of the total pertussis mortality in that year. As a recent M.R.C. trial[2] showed that the newer antibiotics are of little overall value in treatment, this loss of young life surely represents a great challenge to preventive medicine.

The meeting on immunization of young children at the Whittington Hospital, reported in your issue of November 7 (p. 1045), emphasized our incomplete knowledge of the response of young babies, and the duration of their protection, after immunization in the first six months of life. Work has already been done in various countries on interference with diphtheria immunization in young babies inheriting passive antitoxin from their mothers. A paper awaiting publication in your *Journal* deals with immunization of young babies with a very potent diphtheria prophylactic: the clinical work was done at University College Hospital, and the laboratory side at the Wellcome Laboratories. A good deal of additional work has been done here using combined prophylactics. In contrast, very little is known about

the effectiveness of early *H. pertussis* vaccination, and nothing short of a field trial commencing in early infancy would provide a certain answer. An an alternative measure, 1,000 babies immunized recently at University College Hospital with *H. pertussis* vaccine in the first three months of life are being followed up by questionary to parents at yearly intervals, with clinical confirmation and bacteriological control wherever possible. It is hoped to investigate a comparable control group of unimmunized babies, with the help of local authorities. A number of laboratory tests, including serum agglutinins, have been carried out on this group of babies by Dr. J. Ungar, of Glaxo Laboratories, three months after completion of primary whooping-cough immunization. The significance of laboratory tests as proof of acquired immunity against *H. pertussis* is still debated, but their interpretation will be reported later with clinical comparison.

I feel sure that until the problem of the effectiveness of early whooping-cough immunization is solved it will be impossible to decide upon the optimum age to commence immunization with combined prophylactics.—I am, etc.,

London, W.C.1. NEVILLE BUTLER.

REFERENCES

[1] *The Registrar General's Statistical Review for England and Wales, 1950*, p. 390. H.M.S.O.
[2] *Lancet*, 1953, **1**, 1109.

## B.C.G. Vaccination

SIR,—I have read with great interest Dr. J. Lorber's article, "The Mortality from Childhood Tuberculosis in Sheffield" (*Journal*, November 21, p. 1122). It is an excellent record of valuable and instructive work. I would, however, from our experience in Jersey with B.C.G., contest his tentative conclusion that mass B.C.G. vaccination of children may not be necessary. Of his 1,164 children vaccinated and allowed to resume contact with known cases of tuberculosis, not one has developed clinically or radiologically detectable tuberculosis.

We have vaccinated 3,186 children under 5, mostly without any known contact. None of these has developed any form of tuberculosis so far. It now happens occasionally when we find a new case of tuberculosis we also find that the children have already received B.C.G. No doubt the excellent care of tuberculin-positive children known to be contacts and their treatment on the earliest of symptoms have shown excellent results, but surely it is better to vaccinate all children at birth and never have to treat any for either meningitis or miliary tuberculosis, even in these days of streptomycin and isoniazid. We now vaccinate over 75% of our newborn babies in Jersey. The only possible reason against this is fear of the reaction to B.C.G. From our experience we can say that this fear is groundless.—I am etc.,

Jersey, C.I. R. N. MCKINSTRY.

## Acute Appendicitis in Infancy and Early Childhood

SIR,—After reading Mr. G. L. Bunton's article on this subject (*Journal*, July 11, p. 71) we drafted a letter to the Editor venturing to disagree on a few minor points. Like many such letters, it was never posted. Your annotation (*Journal*, November 21, p. 1148), however, stirs us to point out that the results in certain large children's hospitals are scarcely so depressing as your annotation would suggest. Since 1930 one surgical unit of the Royal Hospital for Sick Children has been continuously under the charge of one of us, and accurate records of some 3,000 cases of *acute* appendicitis in infants and children are therefore available, and our opinions are based on this personal experience.

The incidence of acute appendicitis in childhood as seen in this hospital has varied little during these 24 years. There appears to have been some change in the age incidence during recent years. From 1930 until 1948, 7% of cases occurred during the first three years of life; during the following three years the incidence rose to 16%[1] and this increase has been maintained. As you point out in your annotation, the diagnosis of appendicitis in the young child has always been a difficult problem. In this hospital catarrhal appendicitis has always been rare and in 90% of cases the lesion is obstructive. In all age groups dealt with in the hospital (up to 12 years), local or diffuse peritonitis was present in over 60% of cases. In children under the age of 3 years, local or diffuse peritonitis was present in over 90%. As Mr. Bunton says, the condition is neither "rare" nor "very uncommon." In this young age group severe abdominal pain is uncommon but the child usually conveys to the parents that he has pain or discomfort in the abdomen. In our cases 25% had a history of constipation, while 20% had a history of diarrhoea. Purgatives had been given in 35%. Despite the commonly accepted teaching, the omentum frequently exercised its function in young children and in 44% of cases of complicated appendicitis under the age of 3 years the infection was adequately localized. In our experience the appendix was most commonly found in the retrocaecal position. During the past three years the position of the appendix has been noted in almost every necropsy in the hospital. The organ has been retrocaecal, retrocolic, or retro-ilial in over 70% of bodies examined.

Since 1947 antibiotics have been given to patients suffering from severe toxaemia—penicillin from 1947 until 1949; aureomycin, chloramphenicol, and terramycin since 1950. In our experience aureomycin is the most effective antibiotic at present available in combating the toxaemia of peritonitis. Since 1946 the mortality in acute appendicitis in this hospital has varied between 1% and 2%, and during the past four years all deaths have occurred within 12 to 18 hours of admission to hospital, that is to say, from a fulminating toxaemia. All deaths have occurred in patients suffering from diffuse peritonitis. There is no routine incision when operating on cases of appendicitis in childhood. The incision is placed to give the most direct access to the focus of infection. We would suggest that part of the credit for any improvement in results which has occurred in recent years is due to the great advances in paediatric anaesthesia.

The diagnosis of appendicitis is made too late in the young child, and the chief reason for delay in diagnosis is failure to suspect appendicitis in children under 3 years of age. In Glasgow since 1934 surgical paediatrics has been taught as a clinical subject in the medical curriculum, and has been included as part of the final examination in surgery. It is possible that this practice is bearing fruit in this area.—We are, etc.,

MATTHEW WHITE.
Glasgow, C.3. WALLACE M. DENNISON.

REFERENCE

[1] Dennison, W. M., and MacPherson, D. A. (1952). *Glasg. med. J.*, **33**, 175.

## Partial Hepatectomy

SIR,—I was very interested to read the article on partial hepatectomy by Sir Heneage Ogilvie (*Journal*, November 21, p. 1136), as I had heard some time back from Sir Heneage of the technique he used in removing the neoplasm from the liver by means of a pair of closed artery forceps. Recently a case presented itself with a solitary secondary deposit in the liver, and, remembering the technique which I had heard described by Sir Heneage, I was able to apply this method with success.

Briefly (without reference to the notes of the case), the patient was a man in the middle sixties, with a carcinoma of the transverse colon with one secondary deposit in the left lobe of the liver about the size of a plum. A right hemicolectomy was performed, and following this the growth from the liver was removed, according to the technique described in Sir Heneage's article. The point I want to bring out here, and which impressed me most, was the ease with which I was able to cut through the liver substance with the closed artery forceps without undue loss of blood. As one teased the liver substance down into its depth one came across strands of tissue which offered some resistance to the dissection with the forceps. These may have been blood vessels or interlobular septa. As these strands were encountered they were caught in the jaws of the artery forceps and diathermied. Thus, by a process of teasing with the closed Spencer Wells, diathermy the supposed blood vessels, the growth was gradually dissected away from the liver. The large gap left in the liver substance was packed with gelatin sponge and no drainage was instituted. One other factor which may have been of use in lessening the blood loss was the use of hypotensive anaesthesia. Although I am not an advocate of this type of anaesthesia in all cases, I do feel that it has its uses in certain

types of operation, and particularly in resection of the liver as described above it may be used with advantage. I realize, however, that I am speaking of the experience of one case only, but I would not hesitate to carry out this method in any further similar cases should they present themselves.

The final paragraph in the conclusion of Sir Heneage's article is one with which I agree whole-heartedly—namely, the gleaning of knowledge from meetings, the discussion of cases with colleagues, and the pooling of ideas with other surgeons. If I had not heard Sir Heneage talking about his experience in resecting the liver as described in his article, I would have hesitated to remove the secondary deposit in the case I encountered recently.—I am, etc.,

London, W.1. MAURICE LEE.

SIR,—I should like to support Sir Heneage Ogilvie (*Journal*, November 21, p. 1136)—though I doubt if he needs any support from me in his efforts to encourage surgeons to remove secondary growths.

I can refer to a man whose left kidney I removed for carcinoma in November, 1949, and who has had metastases successfully excised from his right lung in 1951 and from his right frontal cerebral lobe in 1952. He is well and at work, and was shown to the Section of Urology at the Royal Society of Medicine on November 26.—I am, etc.,

London, S.W.3. A. R. C. HIGHAM.

## Appendix in the Hernial Sac

SIR,—Dr. T. E. Winckworth's case of acute appendicitis in a hernial sac (*Journal*, September 5, p. 567) has brought forth records of similar cases, and Mr. N. N. Iovetz-Tereshchenko, writing from Georgetown, British Guiana, states (*Journal*, November 28, p. 1220) that in the first reported case of survival after removal of a perforated appendix the viscus was found in what was thought to be a strangulated right inguinal hernia. This was R. J. Hall's case published in 1886.[1] Over 100 years before, however, on October 8, 1735, Claudius Amyand successfully removed an acute and perforated appendix from a hernial sac of a boy aged 11 who was a patient in St. George's Hospital. This case has been overlooked by many writers, but it is apparently the first successful appendicectomy to have been performed, and antedates by some 22 years the case of Mestivier, who is so often given credit as the first to have operated for appendicitis. An excellent account of Amyand's case and of what is known of this surgeon is given by P. G. Creese,[2] and in the interests of justice and of British surgery the credit due to Amyand as the first appendicectomist should be more widely known.—I am, etc.,

Cardiff. LAMBERT ROGERS.

REFERENCES

1 *N.Y. med. J.*, 1886, **43**, 662.
2 *Surg. Gynec. Obstet.*, 1953, **97**, 643.

## Weight of British Children

SIR,—In his paper "Changes in Mean Stature and Weight of British Children over the past Seventy Years" (*Journal*, October 24, p. 897) Dr. E. M. B. Clements states that "weight differences between comparably aged boys of the three income groups have now been eliminated." From the definitions he gives of income groups this means that children of semi-skilled and unskilled workers have now the same weight as children of professional workers.

This conclusion is counter to our experience. In a survey made in 1946–9[1] we found differences of about 6–7 lb. (2.7–3.15 kg.) at 10 years and 12 lb. (5.4 kg.) or more at 15 years between boys attending local authority schools in poor neighbourhoods and those attending independent schools. In another survey in 1950[2] we found consistent differences in the weight of boys of different Registrar-General's social groups and between boys attending public schools, secondary grammar, and modern schools. Thus, at the age of 14 there was a difference of about 10 lb. (4.5 kg.) in weight between the public school and secondary modern school boys.

Data on the weights of children are presented in the annual reports of a number of school medical officers. For Sheffield and Liverpool data are presented separately for children attending schools in good and poor neighbourhoods. In the latest returns to hand for Sheffield (1952) boys aged 5–15 attending schools in good neighbourhoods were 1½–6 lb. (0.67–2.7 kg.) heavier than those attending schools in poor neighbourhoods, and for Liverpool (1950) boys aged 5, 8, and 12 attending schools in good neighbourhoods were approximately 3, 4, and 5 lb. (1.35, 1.8, and 2.25 kg.) heavier than boys of the same ages attending schools in poor neighbourhoods.—We are, etc.,

W. T. C. BERRY.
E. R. BRANSBY.
W. H. HAMMOND.

London, W.1.

REFERENCES

1 Hammond, W. H. (1953). *Brit. J. soc. Med.* In press.
2 Berry, W. T. C., *British Medical Journal*. In press.

## Taking Swabs for Ova of Parasites

SIR,—May we suggest an emendation of the otherwise excellent article by Professor R. Cruickshank on taking swabs in your issue of November 14 (p. 1095)?

The perianal swab referred to is used for collection of threadworm (not roundworm) ova. Roundworm ova are better looked for in the stools. This (N.I.H.) perianal swab, however, has certain disadvantages. The materials for making it are not easily available to the general practitioner, the technique of application and examination is less simple, and the general reliability is less[1] than the adhesive "cellophane" tape method.[2] An illustrated description of the technique shows how convenient it is.[3] If clean lengths of tape, with ¼ in. (0.6 cm.) turned back to give an end to get hold of, are applied to a set of glass slides, the patient or his parent can take the swabs at home first thing in the morning, before the perineum is washed.—We are, etc.,

JOHN M. WATSON.
RONALD MAC KEITH.

London, S.E.1.

REFERENCES

1 Watson, J. M., and Mac Keith, R. (1952). *Arch. Dis. Childh.*, **27**, 526.
2 Graham, C. F. (1941). *Amer. J. trop. Med. Hyg.*, **21**, 159.
3 Mac Keith, R., and Watson, J. M. (1948). *Practitioner*, **160**, 264.

## Use of Obstetric Forceps

SIR,—Perhaps you would allow a word of support for Dr. M. W. Fordham's defence of axis-traction forceps (*Journal*, November 21, p. 1159). Professor T. N. A. Jeffcoate (*Journal*, October 31, p. 951) majestically dismisses them—presumably as scrap iron—but without giving any reason, and yet the usual argument that their use invites the application of excessive force is really a fallacy. Any fool can exert violent traction with any kind of forceps, and on the whole it is probably less likely to do damage if, as Dr. Fordham points out, the line of traction is correct. It would be about as reasonable to suggest that a surgeon should always use a blunt scalpel rather than a sharp one on the grounds that he might do more damage by going too deep with the latter. After all, it is still possible, even in obstetrics, to proceed *secundum artem*. I always apply the axis-traction rods on the principle that, if one is completely familiar with their use in the easy case, their application adds no embarrassment in the difficult one (e.g., when one has performed manual rotation in a persistent occipito-posterior position).

There is a further comment which should, I think, be made in respect of Professor Jeffcoate's article. In referring to the dangers associated with anaesthesia in forceps delivery, he mentions six maternal deaths in the Liverpool Maternity Hospital, three of which were the result of the inhalation of vomit during the induction of general anaesthesia. It would be of great interest to know whether these patients were in the lithotomy position, which we know Professor Jeffcoate favours for all operative deliveries (*Journal*, June 10, 1950, p. 1359). At the time I ventured to challenge his advocacy of the lithotomy position, and pointed out that

the "left lateral position (which often with advantage becomes semi-prone on an ordinary bed) has most distinct advantages in preventing the very real risk of inhalation asphyxia, or pneumonia" (*Journal*, July 1, 1950, p. 47).

It would also be of interest to know what anaesthetic was used in the fourth case where a fatal result occurred "owing to the effect of an anaesthetic on a diseased heart."—I am, etc.,

London, N.W.7. A. H. MORLEY.

## Mitral Stenosis

SIR,—The successful relief of mitral stenosis by valvotomy surely presents the physician with a challenge to find a means of preventing its occurrence in the first place. At a time when there is a tendency for advances in medical therapeutics to oust surgical treatment in a number of diseases, it is disappointing that the surgeon must be asked to rectify the sequelae of our inability to treat rheumatic fever adequately.

I do not know to what extent the use of antirheumatic drugs, such as cortisone and phenylbutazone, in the treatment of rheumatic fever may contribute to prevention of mitral deformity. However, one wonders whether some use might not be made of the knowledge of the pathogenesis of the condition as outlined in your leading article (*Journal*, November 14, p. 1090). If the main cause of valvular fusion is fibrin deposition, might this not be prevented by anticoagulant therapy in the acute stage of rheumatic fever? Indeed, the hypoprothrombinaemic action of salicylates may, in fact, contribute to their therapeutic effect; and the coadministration of vitamin K would then seem to be contraindicated.

Certainly in these days of safe and controllable anticoagulant therapy there would seem to be no reason against a trial of the latter in rheumatic fever.—I am, etc.,

Twickenham. DAVID WHEATLEY.

## Insulin Zinc Suspensions

SIR,—I have been much interested in the articles by Drs. Wilfrid Oakley, Ian Murray, and Robert B. Wilson about the new suspension insulins (*Journal*, November 7, pp. 1021 and 1023). We have been using "lente" insulin at the two diabetic clinics in Brighton, but were rather handicapped by a hiatus in supplies, and by the fact that the strength 80 units to the ml. has only been available lately. Since the reputed action of lente insulin seemed comparable with that of globin—a supposition confirmed by Dr. F. Gerritzen (*Journal*, November 7, p. 1030)—our experience with this insulin may be of interest.

Twenty out-patients, 9 men and 11 women, reasonably well controlled on globin insulin, were given the same or a rather larger dose of lente insulin. An average of three previous blood sugar estimations, taken three and a half to four hours after breakfast, was compared at fortnightly intervals with the blood sugar and clinical state while on lente. The results were as follows:

*Better.*—Four patients, for whom the dosage of globin varied from 28 units to 60 units. Three reported absence of or milder insulin reactions and one the absence of painful lumps at the site of injection; one needed the same dose of lente, two 6 and 8 units more respectively, and one 6 units less. The absence or reduction of reactions was associated with blood sugar levels higher than the previous average in three cases. *The Same.*—Ten patients. Three needed the same dose of lente and seven larger doses, the increase ranging from 6 units to 32 units—for example, from G. 36 to L. 64. *Worse.*—Six patients. One had a severe reaction at 1.30 a.m. and needed less lente than globin (average blood sugar on G. 56, 114 mg. per 100 ml., and on L. 48, 75 mg. per 100 ml.). In four patients there was a disconcerting loss of control. One schoolgirl of 13 years who had been steadily controlled on globin insulin since February, 1952, was transferred from G. 60 to L. 64 and admitted 12 days later in diabetic ketosis. Two women on G. 32 and G. 18 units respectively had severe diabetic symptoms on doses of lente increased by 6 units. These two patients did not wish to continue lente, but could probably have been controlled on larger doses. One patient had been diabetic for over 25 years, is active, and of the unstable type. He has been balanced for several years to his own satisfaction on globin insulin and he is able to take his own blood for sugar estimations. On transferring to the same dose of lente insulin he became an uncontrolled diabetic with thirst, polyuria, and lassitude. He lost weight and "felt his legs weak and heavy." He refused to continue, since his diabetic symptoms persisted on a dose increased by 50%. The last patient, a woman of 50, had been for some time unsteady on globin in varying doses. It was hoped that on lente she would be better, but after consistently high blood sugar readings without symptoms—that is, over 250 mg. per 100 ml. throughout the day—she went into a severe hypoglycaemic reaction in the small hours of the morning.

In patients previously taking other insulins, protamine zinc and soluble, protamine zinc alone and two doses of soluble insulin, the transfer was associated in several cases with loss of control and the need for greatly increased dosage of lente insulin. One young man of 23, however, who had been poorly controlled on a large and complicated dosage of protamine zinc and soluble insulin, is now comfortable with normal blood sugar on two doses of lente insulin of 72 and 68 units respectively, a considerable total reduction. Four to six weeks has not been long enough to discover any tendency for the insulin demand to become less; presumably, if so, hypoglycaemic reactions will occur.

The following tentative conclusions emerge: (1) Similar control can be obtained with lente as with globin, though in perhaps half or more of the cases larger, sometimes much larger, doses of lente are needed. (2) Severe insulin reactions do occur with lente, and when they are abolished it may be at the expense of an increased average blood sugar. (3) The transfer from the old types of insulin to lente is attended with some danger, and closer supervision than we have undertaken is desirable. (4) The absence of local reactions is constant, though these are abolished also with protamine zinc insulin and globin insulin if nurses and patients can be induced to deliver the insulin sub- instead of intracutaneously; they are rarely due to true allergy, but usually to the irritating properties of the protamine when injected into the skin. I hope that our old "standby" soluble or regular insulin will always be available, though I should like the strength 20 units to the ml. to be discontinued.

Further study is needed to determine whether lente and ultralente should replace globin and protamine zinc insulin respectively, but confusion will indeed be worse confounded when all these insulins are on the market.—I am, etc.,

Hove. G. M. WAUCHOPE.

SIR,—Drs. A. Stuart Mason and D. Verel in their letter (*Journal*, November 28, p. 1215) attribute to me the suggestion that globin and protamine zinc insulins should be withdrawn. If they will refer to my article they will see that in point of fact I made no such foolish, unqualified suggestion. What I did say was: "We feel that further knowledge is required to determine whether or not ultralente has, for practical purposes, the same action as P.Z.I. and semilente the same action as globin insulin; if this is shown to be the case then it would seem reasonable to suggest that, if and when these two insulins of the lente series are put on the market, P.Z.I. and globin insulin should be simultaneously withdrawn so as to lessen the confusion which would inevitably result from having seven insulin preparations available to doctors and patients at one and the same time."

If Dr. Mason and Dr. Verel do not agree with the suggestion in its full form, I can only conclude that they are in favour of retaining four insulin preparations when the same therapeutic action can be obtained with the use of two.

Drs. R. Powell and S. Bradshaw in their letter in the same issue (p. 1216) defend the marketing of semilente and ultralente insulins on the ground that a few diabetics may benefit from their use. These doctors, however, do not have to treat large numbers of diabetics, and I would refer them to the letter in the same issue by Dr. R. D. Lawrence (p. 1215), in which he rightly draws attention to the fact that a very large number of doctors who do treat diabetics agreed unanimously that only one of the new insulin preparations should be introduced at present.—I am, etc.,

London, W.1. WILFRID OAKLEY.

SIR,—I agree entirely with Dr. R. D. Lawrence (*Journal*, November 28, p. 1215). In my own department I have already encountered patients who have been supplied with insulin zinc suspensions ("semilente" or "ultralente") where only insulin zinc suspension "lente" has been advised. I

feel that insufficient stress has been laid on the important differences in duration of action of the three I.Z.S. preparations, and that only one type of I.Z.S.—namely, lente—should have been generally supplied to the public, according to the recommendations made at the Diabetic Association conference last July in Leeds.—I am, etc.,

Birkenhead. A. GRUNBERG.

## Malaria in Ex-Servicemen

SIR,—With reference to Dr. I. B. Munro's letter on malaria in ex-Servicemen (*Journal*, December 5, p. 1269), in which it is suggested that my recommendations for the treatment of vivax malaria (*Journal*, October 27, 1951, p. 1021) differ from those put forward by Sir Neil Hamilton Fairley (*Journal*, November 21, p. 1157), I would point out that Sir Neil's remarks were directed specifically to cases of malaria occurring in this country among persons no longer exposed to reinfection, under circumstances where treatment could be properly supervised.

The Refresher Course article to which Dr. Munro refers, on the other hand, was intended for doctors practising in any part of the world under a great variety of circumstances. In stating that the routine administration of the 8-aminoquinolines in *all* cases of vivax malaria is not recommended I had in mind such considerations as the following: (1) The patients might be either non-immune immigrants or indigenous inhabitants of malarious areas possessing varying degrees of premunity. They might be long-term residents exposed to repeated reinfection, or persons who had returned from malarious areas and were now no longer so exposed. They might also be casual dispensary patients whose treatment it would be impossible to supervise. (2) It is not safe to give any of the 8-aminoquinoline drugs without medical supervision, because of the occasional unpredictable occurrence of dangerous toxic side-effects which call for immediate cessation of treatment. This applies particularly to members of dark-skinned races. (3) There are certain strains of *Plasmodium vivax* which do not give rise to late relapses—e.g., the so-called Chesson strain originating in New Guinea.

I would not recommend the administration of the 8-aminoquinolines (*a*) to persons exposed to repeated reinfection, (*b*) to the partially immune indigenous inhabitants of malarious countries, (*c*) in areas where it is known that the local strains of *P. vivax* are not associated with late relapses, or (*d*) under any circumstances where medical supervision throughout the course of treatment was not possible.

Regarding Dr. Munro's allusion to vivax malaria contracted in Korea, late relapse is a common feature of infections incurred in that country. In the summer of 1951 and 1952 the number of malarial attacks in men brought back from service in Korea to the United States was in the neighbourhood of 600 per week in military installations alone. The routine administration of primaquine during the 14 days' voyage from Korea to America has brought down this figure to insignificant proportions.

May I add that I am in entire agreement with the views put forward in Sir Neil's letter?—I am, etc.,

Horton. G. COVELL.

## Overseas Service

SIR,—I would like to comment on Mr. Ian Fraser's article (*Journal*, October 31, p. 987) and on the three letters on the same topic (*Journal*, November 28, pp. 1216–17).

My first point is that a specialist service is not "priority No. 1" in the Gold Coast. Do I, an African, have to remind British doctors of the work of their compatriot, Edwin Chadwick? The first foundation of health in the Gold Coast is not the work of the hospital doctor, least of all the highly qualified specialists in ophthalmics or orthopaedic surgery; it is the work of the general practitioner in the villages in conjunction with other public health workers. The major health problems of the Gold Coast, the diseases which are most widespread and damaging in their effects, are those which can be tackled only through a public health programme. A magnificent new hospital costing £5,000,000 may be very necessary, but it will make no impression on a village without latrines, with a polluted water supply, and with no adequate provision for the disposal of either household refuse or of the very people themselves after death. I am not saying that the Gold Coast does not need specialists; but I am saying that the most up-to-date hospitals staffed with the most highly qualified specialists will not, in themselves, diminish the maternal and infantile death rates, and the incidence of yaws, hookworm, malaria, and nutritional disorders which are the real challenge to the medical profession in the Gold Coast to-day.

While I would agree with Mr. Fraser that there is more than enough work in the Gold Coast to occupy all British applicants, I think they should understand what they will be called upon to do. It is rarely that a specialist can devote his time to his specialty as his colleague does in Britain, because, in the absence of a general-practitioner service, there is no one but the specialist to cope with the minor and routine complaints. Many cases now demanding so much of the specialist's time in out-patient clinics and in the wards would not need to go to hospital at all if an effort were made to establish doctors in the villages. As long as the emphasis is placed on specialists in hospitals instead of on general practitioners in villages, the specialists will be faced with work outside the range of their specialties and frustrated by the high proportion of cases which arrive in hospital when they are beyond help. Lack of general practitioners defeats the purpose of specialists.

Turning now to African doctors, I wonder if Mr. Fraser has really understood their position. As Dr. K. A. Taylor suggested in his letter (*Journal*, November 28, p. 1217) our numbers have been seriously restricted by the failure of past Governments to give more than an average of one medical scholarship a year. Even when we qualified, we were not sure of immediate employment as a result of a ratio policy whereby African medical officers were employed in a strict, and very small, proportion to the expatriate officers. If we have been reluctant to go home it has only been because we wanted postgraduate experience, and many have gained this extra knowledge in the teeth of strong opposition from past Governments. The three (not two as stated by Dr. Taylor) who have stayed in this country did not do so originally from choice. They all had to take posts in Britain while waiting for the Gold Coast Medical Department to offer them jobs, and now, having become established, two in general practice, one as a surgeon, they are faced with problems of salary and future security similar to those of their British colleagues in the colonial service. Each would face a substantial drop in salary and little credit for considerable experience gained in Britain. The general practitioners, as "non-specialists," would receive salaries less than those of an expatriate midwife or, in some cases, of expatriate clerks.

The health needs of the Gold Coast can be tackled only by a bold programme by the Government which will correlate all aspects of life and require the services of general practitioners and ancillary professions as well as those of specialists. Nor must we minimize the part to be played by elected local authorities, for "a healthy nation is not only an asset to, but an advertisement for, democracy."—I am, etc.,

Salford. A. K. KUTA-DANKWA.

## Unwrapping the "Journal"

SIR,—There was a time, not so long ago it seems to me, when the wrapping of the weekly *British Medical Journal* carried a device for easy and rapid opening. You pulled a tag and out came the *Journal*, leaving in your hands the envelope in two pieces. Now, failing a special implement, getting at the *Journal* takes some two or three minutes of scratching and clawing, followed by an exasperating hunt for fragments of the envelope and their collection and disposal. Cannot we revert to the ingenious old wrapper?—I am, etc.,

Cross-in-Hand, Sussex. H. LYNDHURST DUKE.

### Conquest of Plague

SIR,—In his review of Dr. Fabian Hirst's book, *The Conquest of Plague*, Sir Arthur MacNalty states (*Journal*, November 21, p. 1143): "In 1894 Kitasato and Yersin independently discovered the bacillus of plague, *Pasteurella pestis*. . . ." Presumably the reviewer took this from the book itself, but, whether he did or did not, it is a pity that this mistake should be perpetuated. The organism described by Kitasato, and at first claimed by him as the cause of plague, was Gram-positive and motile, whereas Yersin's organism, the true *Pasteurella pestis*, is Gram-negative and non-motile. Kitasato himself, at a medical conference in the Far East in 1925, before an audience of 400, announced that the discoverer of what he called the *Bacillus pestis* was Yersin.

Incidentally, some authors state that Yersin was, as was Kitasato, a Japanese. This also is erroneous. Yersin was a Swiss, born at Aubonne on September 23, 1863, was educated at Lausanne, and became a naturalized Frenchman in 1887. —I am, etc.,

Braintree, Essex. H. HAROLD SCOTT.

## POINTS FROM LETTERS

**Old-fashioned Remedies**

Dr. HAROLD H. SANGUINETTI (London, W.8) writes: Much as I appreciate the benefits of the sulphonamides and antibiotics I am not prepared to forgo the use of what this generation probably regards as old-fashioned remedies, and among these I would place salicin, which I now find unobtainable. When I was a student (I qualified in 1897) . . . Dr. Burney Yeo, of King's College Hospital, wrote a *Manual of Medical Treatment*. . . . Writing of the treatment of coryza, Dr. Yeo recommended the following prescription: Sp. aetheris nitrosi dr. 4, liq. ammonii acetatis oz. 2, salicini puri gr. 40, vini ipecacuanha min. 40, aqua camphorae ad oz. 8—sig. an eighth part every four hours. This mixture I have found efficacious if taken at the beginning of a cold. . . . During the 1918–19 influenza epidemic Mr. E. B. Turner, a general practitioner in London and at one time Chairman of the Representative Body, wrote an article, published in the *Journal* (March 18, 1919, p. 278), advocating the administration of large and frequent doses of salicin to influenza patients, maintaining that thereby he kept his patients free from complications. I adopted the treatment, but my cases were too few on which to base an opinion.

**The Cracked Nipple**

Dr. S. G. HAMILTON (Thornton Heath) writes: The cracked nipple is a common and very painful condition, leading sometimes to mastitis, but more frequently to the unnecessary weaning of infants because the mother is unable to tolerate the pain which must recur every four hours. In this connexion, the natural nursing nipple shield deserves to be more widely known. This rubber device fits over and beyond the areolar margin of the nipple, completely protecting the injured nipple from further irritation during the feeds, which can proceed as usual. An antiseptic or antibiotic cream may be applied after the feed as a prophylactic against infection. It is most gratifying to see the immediate relief experienced by the mother, and to mark how quickly the lesion heals.

**Hay-fever and the Common Cold**

Dr. A. E. BERNSTIEN (Liverpool, 1) writes: For the past few years I have been regularly told by patients suffering from perennial or annual hay-fever that for some reason or other they do not appear to get the common cold. . . . It is not difficult to check up on such cases. The patient with annual or perennial hay-fever has a typically pale, boggy mucoperiosteum, in severe cases the conchae being so swollen, although exhibiting great pallor, that they completely obstruct the nasal airway on one or both sides. In acute attacks there is profuse, thin, watery discharge, with sneezing due to highly sensitive trigger areas, discharge and injection of the eyes, and showing positive skin reactions to pollens, dust, etc. In the common cold the lining of the nose is red and angry looking, and no eosinophils can ever be found by smears as they can in large numbers during attacks of hay-fever. Whether the allergic hay-fever individual's resistance to the common cold virus is local to the nasal mucosa or whether it is a general one such as a blocking antibody in the blood stream is a matter for discovery. It is noteworthy that people suffering from hay asthma without hay-fever, and who reveal a blood eosinophilia, still get coryza as often as those who have no asthma.

# Obituary

### T. W. LUMSDEN, M.D.

Dr. T. W. Lumsden, who was at one time director of cancer research at the London Hospital, died at Stocking Pelham, Hertfordshire, on November 24 at the age of 78.

Thomas William Lumsden was born on December 20, 1874, the son of the Rev. Edward Lumsden. From Aberdeen Grammar School he went on to study medicine at Aberdeen University, where he was awarded the Fife Jamieson gold medal in anatomy in 1895 and graduated M.B., Ch.B., with honours, in 1897, in which year he also won the Shepherd Memorial gold medal in surgery. Two years later he gained the Struthers gold medal and prize in anatomy, and in 1901 he proceeded to the M.D., receiving a commendation for his thesis. After holding resident appointments at Aberdeen Royal Infirmary Lumsden became anatomy demonstrator in the university. He then moved south to become registrar at the Central London Throat Hospital. In 1900 he began what was to be a long period in general practice in the West End of London. During these years he was able to find time for some research work at the Lister Institute, and it came as no surprise to his friends when in 1926 he relinquished his practice to join the staff of the Lister Institute as an honorary assistant in the pathological department. At the same time he became a research worker for the British Empire Cancer Campaign, and in 1930 he was appointed director of cancer research at the London Hospital, a post he held until he retired in 1941.

Lumsden's early research was concerned with the centres regulating respiration, but his main interest was in the problem of cancer. He studied particularly immunity to cancer, and his life-long aim was to produce an anti-cancer serum. During his career as a research worker he contributed a number of articles on cancer to scientific journals. Cancer research meant everything to him, but he had other interests. He enjoyed drawing, playing the violoncello, and listening to music. He leaves a widow.

### Sir LANCELOT BARRINGTON-WARD

K.C.V.O., Ch.M., F.R.C.S., F.R.C.S.Ed.

Surgeon Lieutenant-Commander P. D. A. Durham writes: As one of his former house-surgeons at Great Ormond Street I should like to pay a small tribute to the late Sir Lancelot Barrington-Ward, whose obituary notice was printed in the *Journal* of November 28 (p. 1221). His patience and gentleness with young patients were outstanding. Perhaps his most remarkable quality was his punctilious courtesy to all the staff in the operating theatre. He assumed that each would naturally give of his best, and in consequence there was never a tense atmosphere. One gained the impression that he considered temperamental outbursts the result of bad manners and poor surgery. At the same time he held firm views on what he considered was bad technique. I well remember him describing one particular type of operation as not even being worthy of "horticulture." He was a fine surgeon and a great gentleman.

W. B. G. and R. J. McN. L. write: We should like to add a few notes to the obituary notice of Sir Lancelot Barrington-Ward. His death brings to an end, at least for the present, a long connexion between Great Ormond Street Hospital for Sick Children and the Royal Northern Hospital. He was one of those few men who were masters of

surgery in both children and adults, and one of his most notable fields was the surgery of the stomach and gall-bladder. He had probably operated on more cases of congenital pyloric stenosis than any of his contemporaries, and here his gentle touch and scrupulous technique were seen to perfection. Also he was one of those very few general surgeons who performed tonsillectomy at any age with less post-operative discomfort than most, and many were the doctors, their wives, and their families who knew of this and took advantage of his skill. His writings are well known, especially his *Abdominal Surgery of Children*, and he was the editor of two editions of *The Royal Northern Textbook of Operative Surgery*.

Barrington-Ward possessed a critical mind allied with sound judgment, and in committee this was invaluable, not only in maintaining good relations between the medical and lay bodies but also in dealing with the difficult problems which arose. His opinion was always sound, and was usually accepted.

Since his retirement a year ago he had been much missed, as he was active and full of enthusiasm up to the last, and it is a sad turn of fate that he was not spared longer to enjoy his retirement at his farm in Suffolk, to which he had latterly devoted so much time and interest. The entire staff of the Royal Northern Hospital would wish to join with us in a tribute to an honoured, valued, and dearly loved friend and colleague.

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Dr. HUBERT HARRY HOLLICK died at his home at Ashbourne, Derbyshire, on November 8, shortly after his retirement, at the age of 76. Born on July 30, 1877, he was educated at King Henry VIII School, Coventry, and later entered Queen's Hospital, Birmingham, as a medical student and qualified M.R.C.S., L.R.C.P. in 1899. After completing his appointment as house-surgeon at the Queen's Hospital, he served in South Africa as a civil surgeon in a hospital in Ladysmith. When the siege was raised he was posted to a hospital train, but he suffered a severe attack of typhoid fever, and when convalescent was invalided home. A quiet life, however, was not for him, for after serving for a time as a ship surgeon he went to Australia and was appointed superintendent of the leper colony at Stradbroke, Queensland. In 1905 he returned to this country and settled at Ashbourne in partnership with the late Dr. E. A. Sadler. His practice was small to start with, but by hard work, good clinical knowledge, keen observation, and the care he took of his patients he rapidly increased their number until he had one of the best practices in Derbyshire. Thus he was able to take his son, Dr. J. R. Hollick, and another doctor into partnership. He had a flair for learning the history of his patients, and it was a real pleasure to consult with him, for one learned much. He was so engrossed in and fond of his work that as time went on he disliked taking holidays away from his practice. He was a very quick worker and many stories were told about him. When on his rounds he did not as a rule wait until his car stopped before he alighted. He had previously instructed his chauffeur to drive on directly he heard the door bang. Unfortunately one day the door banged accidentally before he got in. The car started and Dr. Hollick was left by the roadside, his chauffeur not noticing the mistake until he had gone some miles. In spite of a very busy practice, Dr. Hollick found time to act as medical officer to two local Red Cross hospitals in both wars, work he did with enthusiasm. He was also for many years medical officer of health to the Ashbourne urban and rural and district councils, as well as police surgeon. His work left him little time for hobbies. Nevertheless he was a keen and good gardener, as those who saw his garden would agree. He kept pigeons and used to race them, and in earlier life he was a keen shot. In 1910 he married Miss Edith Lyon, and he is survived by his widow, a daughter, and a son, who is in his father's old practice. At the funeral service, Ashbourne Parish Church was full to overflowing with people, mainly patients of his, who came to honour him and to pay their last respects.—F. G. L.

We are indebted to Dr. R. S. FREW for the following appreciation of Dr. ALICE HUTCHISON, whose obituary notice was published in the *Journal* of November 7 (p. 1052): Dr. Alice Hutchison was a clinical assistant to me for most of the time I was out-patient physician at Great Ormond Street, and a good clinical assistant she was. Always punctual, she was keen and eager as if each session was the first she had ever attended. Kind to and patient with the mothers and children, she had their confidence and affection—earnest and compassionate when necessary, laughing when that best met the case. Frequently addressed by the mothers as "Yes, nurse," "No, nurse," she never corrected them, but when a peculiarly flagrant instance occurred she would catch my eye and smile, so that I too might enjoy the joke. She had a kind heart and has left me with a happy memory of her.

# Medical Notes in Parliament

## SEXUAL OFFENCES

Sir ROBERT BOOTHBY asked the Home Secretary on December 3 if the Government would recommend the appointment of a royal commission to examine the law on sexual offences and the treatment of adult sexual delinquents, with particular reference to homosexuality, and to make recommendations on the changes desirable in the light of modern scientific knowledge and of recent discoveries in psychology and psychiatry.

Sir DAVID MAXWELL FYFE stated that the general question of the law and treatment relating to sexual offenders was engaging his attention, but he could not yet make any statement.

Sir ROBERT BOOTHBY asked the Home Secretary if he was satisfied that the law was effective and workable, if he was satisfied with present institutional treatment, and if he thought that further research was urgently required.

Sir DAVID MAXWELL FYFE said that as the point had been raised he must make it clear that one element in dealing with the matter was the protective element in punishment, because homosexuals in general were exhibitionists and proselytizers, and a danger to others, especially the young, and he would give no countenance to the view that they should not be prevented from being such a danger. On the point about treatment, he assured the House that they were very much alive to the problem in the prisons, and there were arrangements for medical attention, especially of a psychiatric kind. But the difficulty in these cases was that for treatment to be successful there must be co-operation, and in many cases that was refused. On the third point, it must be borne in mind that, apart from the true invert, there were homosexuals who used that instead of ordinary sexual intercourse, and in addition to them the male prostitutes who came up on importuning cases and the sensationalists who would try any form of excitement and indulgence. These three types, apart from the male invert, he believed could be and were being dealt with by the prison system.

Mr. R. R. STOKES emphasized that the authorities should bear in mind the importance, while respecting the rights of defendants, of reducing to the minimum the publicity and strain imposed on juveniles mixed up in adult cases. Sir DAVID MAXWELL FYFE expressed his entire agreement.

Brigadier F. MEDLICOTT said that public opinion had been at fault for many years in treating homosexuality as a fit subject for music-hall humour. Mrs. E. BRADDOCK said many magistrates were reluctant to give terms of imprisonment because of overcrowding in the prisons.

Sir DAVID MAXWELL FYFE replied that unfortunately there were about 5,000 persons who were three in a cell. The matter had been carefully examined, and he believed the chances of increasing homosexual inclinations from that had been greatly exaggerated. Homosexuality did exist in prisons—Sir Alexander Paterson had said they could not help it in a "monastery of men unwilling to be monks"—but the

effect had been exaggerated. They had not been able to find any evidence of increase of inclination.

In reply to Mr. D. Donnelly, Sir David Maxwell Fyfe said he was willing to meet anyone who had ideas on the matter. But he wanted it to be clear that as Home Secretary he had a duty to protect the people, especially the youth, of the country.

Comparative figures for pre-war and post-war years were given in other replies by the Home Secretary to Mr. W. S. Shepherd. The number of unnatural offences known to the police in England and Wales in 1938 was 134, the number of attempts to commit unnatural offences (including indecent assaults on male persons and cases of importuning for immoral purposes dealt with on indictment) was 822, and the number of offences of gross indecency was 320. The corresponding figures for 1952 were 670, 3,087, and 1,686. Similar figures for offences of male importuning dealt with summarily were not available. Sir David Maxwell Fyfe added that there was no reason to think that the penalties were inadequate. Speaking from memory, he said that in 1952 there were 5,443 offences, and about 600 offenders were sent to prison.

The London figures for 1952 were: unnatural offences, 36 prosecutions and 35 convictions; attempted unnatural offences, etc., 144 prosecutions and 135 convictions; gross indecency, 121 prosecutions and 113 convictions. In addition, summary proceedings were instituted against 373 persons for importuning and 196 under local regulations for indecency in parks and open spaces, but there was no record of the number of convictions.

### Fluoridation of Water Supplies

Mr. H. PRICE asked the Minister of Health on December 3 what action he proposed to take regarding the recommendations of the report of the United Kingdom mission which studied the fluoridation of domestic water supplies in North America as a means of controlling dental caries. Mr. IAIN MACLEOD stated that the Government had decided to accept the recommendations of the mission. In conjunction with the Minister of Housing and Local Government, who was responsible for public water supplies in England and Wales, the Secretary of State for Scotland and he proposed to arrange for studies to be made in some selected communities of the various aspects of the fluoridation of water supplies before considering whether fluoridation should be generally adopted in this country. An approach would be made to certain local authorities to invite their co-operation in making these studies.

### Private Patients' Prescriptions

Mr. W. ROBSON-BROWN asked the Minister of Health on December 3 what were the reasons which prevented persons who subscribed to the National Health Scheme, but who for personal reasons desired to be treated as private patients, from obtaining medical prescriptions from their doctors under the provisions of the National Health Act. Miss PAT HORNSBY-SMITH, the Parliamentary Secretary, stated that the National Health Service Act, 1946, provided for the supply of drugs and medicines only to persons receiving general medical services and general dental services under the Act.

### Food and Health

Dr. BARNET STROSS, speaking in the debate on the Supplementary Estimate for the Ministry of Food on December 2, expressed his regret at the impending demise of the Ministry. Its work, he said, had been of the greatest value to the country. The benefits that had sprung from it were based on knowledge gained only in this century, and really in the past 30 years, and by advisers of the quality of the late Sir Jack Drummond. Improvements in the national health during the past 30 years had not been the responsibility of medical science alone, but had been in part at least due to improved knowledge about nutrition, and what the Ministry of Food had done to improve nutrition since its inception. It had brought about bread of better quality, and more milk, and "fair shares" during a time of great stringency. Milk consumption now was nearly 60% more than before the war. Coarse bread was not palatable, but the people did their best to get used to it. Simple things like that had made a great difference to health.

He quarrelled with the provision in the Estimate for increased expenditure on the things in plentiful supply before the war—chops, steaks, and cadaver generally—the smaller expenditure on the health foods, particularly milk and milk products. Dr. Stross supported a suggestion that the milk surplus should be evaporated and packed in containers, so that it could be put into consumption again.

### Proposals for "Smog"

The Government proposals for giving effect to the interim report of the Beaver Committee on air pollution (see p. 1332) were declared on December 2, concurrently with the issue of the report.

Mr. HAROLD MACMILLAN, Minister of Housing and Local Government, in a statement to the House of Commons, said that the Government had already arranged for the Meteorological Office to issue through the usual channels warnings when serious fog was expected to prevail for at least 24 hours in areas of normally high pollution. Householders in large towns who were dependent on solid fuel should lay in a stock of, say, one hundredweight of coke or other smokeless fuel for use in periods of persistent fog.

Smoke-control measures in industry, shops, etc., should be brought up to peak efficiency at once and checked at frequent intervals throughout the winter. The Government was studying further steps which might be taken to ensure application of these measures and make them more effective, while awaiting the next report of the Beaver Committee.

## Medico-Legal

### ANAESTHETIST NOT NEGLIGENT

The Court of Appeal on December 7 set aside judgment awarding £4,000 damages to Mr. R. J. Crawford against Charing Cross Hospital. Mr. Crawford had alleged that damage to his left arm during an operation was caused by negligence of the anaesthetist.[1] The anaesthetist had administered a blood transfusion, and the judge had held he had been negligent in not avoiding excessive extension of the patient's arm and that the negligence had contributed to the very severe degree of brachial paralysis that was left.

Lord Justice Somervell said[2] that two questions arose in the appeal—whether the particular treatment of the plaintiff's arm caused or contributed to the brachial palsy and whether that treatment constituted negligence on the part of Dr. Clausen, the anaesthetist. In about ¼% of such operations brachial palsy followed, and generally it was not permanent. The evidence given by the medical experts showed no negligence by Dr. Clausen, but the judge had based his judgment on Dr. Clausen's failure to read an article in the *Lancet*. Lord Justice Somervell said it was quite impossible to support the judgment, and he had no hesitation in holding that there was no evidence of negligence.

Lord Justice Denning said[3] that every mishap in a hospital did not put upon the hospital the burden of an explanation. So many serious risks were involved in treatment, especially a major operation, that mishaps occurred without any negligence at all. The burden of explanation was not put on the hospital unless it was quite clear that something had gone seriously wrong. It had been proved here that all reasonable care was taken at the hospital. This was just a

[1] *British Medical Journal*, May 2, p. 1001.
[2] *The Times*, December 8.
[3] *Manchester Guardian*, December 8.

misadventure. He agreed it would be putting much too high a burden on the medical man to say that he must read every article in the medical press.

Lord Justice Romer agreed that the appeal succeeded.

## OVERDOSAGE OF TEETHING POWDERS

At an inquest on a 10-months-old girl held on December 2 at Stoke-on-Trent a verdict of misadventure was returned. The jury decided that the cause of death was bronchopneumonia due to pink disease due to mercury poisoning following an innocent overdosage of teething powders. They added a rider that they considered packets of teething powder should in future be divided at their source into the correct dose according to age.[1]

The girl was admitted to the City General Hospital, Stoke-on-Trent, on October 15 under the care of Dr. J. G. Dathan. He obtained a history from the child's mother that teething powders had been administered regularly during the previous six or seven months to a total of some 64 powders or more. A specimen of urine showed 3,900 μg. of mercury per litre. This was the highest figure Dr. Dathan had ever received. Clinically the child was suffering from pink disease. In spite of treatment, she died on October 23 from pneumonia, a result of the pink disease.

At the necropsy, carried out by Dr. C. Giles, the cause of death was confirmed as bronchopneumonia due to pink disease, and investigations carried out at the West Midland Forensic Science Laboratory showed the following mercury contents of specimens taken from certain organs: liver, 1.8 mg. per 100 g.; kidney, 3.4 mg. per 100 g.; brain, 0.3 mg. per 100 g. An analysis carried out at the County Analyst's Department showed that the amount of mercurous chloride present in a sample of the mixed powders was 26.3%. The amount declared to be present was 26.7%.

It was represented on behalf of John Steedman & Co. that the powders had been sold since 1812 with the same formula. Seven million were sold every year, and 2,000 each day in Staffordshire.

The mother of the dead child said that when the girl was about 2 months old she began giving her half a Steedman's powder each week. At 6 months old she increased it to two powders a week, and at 8 months old she gave three powders every week or ten days.

The coroner quoted the dosages specified on the wrapper as one-third of a powder from 1 to 3 months, half a powder from 3 to 6 months, and one powder only and no more from 6 months to 14 years, and told the jury they might hesitate to believe that these powders were ever intended to be given regularly and frequently, but only as occasion arose. He suggested they might consider that the manufacturers might be well advised to put further and better instructions on the packages.

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Since the inquest reported above was held Messrs. John Steedman and Co. have informed us that they decided some months ago not to market any more teething powders containing calomel. They say that distribution of the new formula began at the beginning of December.

## PSYCHOPATH'S APPEAL DISMISSED

The Court of Criminal Appeal dismissed on December 1 the appeal of J. Francis Wilkinson from his conviction of murdering a 5-year-old girl. For the appellant it was said that both prosecution and defence agreed at his trial that he was a psychopath.[2] Insanity was primarily a question for the jury and should have been left for them, whereas the judge had ruled that there was no evidence that Wilkinson was suffering from a disease of the mind which would bring him within the M'Naghten rules. The Lord Chief Justice said that the judge was right.[3] There was no evidence on which the jury could have found that the man was insane.

[1] *Evening Sentinel*, December 2.
[2] *British Medical Journal*, November 28, 1953, p. 1224.
[3] *The Times*, December 2.

## INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **November 21** (No. 46) and corresponding week 1952.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

| CASES in Countries and London | 1953 Eng. & Wales | 1953 Lond. | 1953 Scot. | 1953 N. Ire. | 1953 Eire | 1952 Eng. & Wales | 1952 Lond. | 1952 Scot. | 1952 N. Ire. | 1952 Eire |
|---|---|---|---|---|---|---|---|---|---|---|
| Diphtheria | 28 | 1 | 3 | 0 | 1 | 44 | 7 | 13 | 0 | 2 |
| Dysentery | 362 | 61 | 177 | 3 | 1 | 211 | 46 | 106 | 1 | 3 |
| Encephalitis, acute | 6 | 1 | 0 | 1 | | 2 | 0 | 0 | 0 | |
| Enteric fever: Typhoid | 2 | 0 | 0 | 0 | | 3 | 1 | 0 | 1 | 1 |
| Enteric fever: Paratyphoid | 9 | 0 | 0 | 0 | | 5 | 0 | 0 | 0 | |
| Food-poisoning | 132 | 23 | | 0 | | 151 | 10 | | 0 | |
| Infective enteritis or diarrhoea under 2 years | | | | 16 | 19 | | | | 7 | 8 |
| Measles* | 793 | 15 | 38 | 16 | 99 | 12,035 | 1208 | 207 | 16 | 130 |
| Meningococcal infection | 36 | 2 | 9 | 1 | | 29 | 4 | 13 | 0 | 2 |
| Ophthalmia neonatorum | 25 | 2 | 5 | 0 | | 29 | 0 | 8 | 0 | |
| Pneumonia† | 583 | 41 | 183 | 8 | 4 | 452 | 36 | 290 | 5 | |
| Poliomyelitis, acute: Paralytic | 54 | 3 | 17 | 2 | 2 | 82 | 11 | 6 | 1 | 4 |
| Poliomyelitis, acute: Non-paralytic | 34 | 4 | | | | 22 | 1 | | | |
| Puerperal fever§ | 223 | 38 | 13 | 3 | 2 | 226 | 20 | 12 | 1 | |
| Scarlet fever | 1,613 | 85 | 268 | 46 | 74 | 2,065 | 180 | 331 | 18 | 135 |
| Tuberculosis: Respiratory | | | 123 | 23 | | | | 138 | 27 | |
| Tuberculosis: Non-respiratory | | | 22 | 3 | | | | 24 | 5 | |
| Whooping-cough | 2,510 | 106 | 318 | 68 | 81 | 1,780 | 113 | 80 | 42 | 64 |

| DEATHS in Great Towns | 1953 Eng. & Wales | 1953 Lond. | 1953 Scot. | 1953 N. Ire. | 1953 Eire | 1952 Eng. & Wales | 1952 Lond. | 1952 Scot. | 1952 N. Ire. | 1952 Eire |
|---|---|---|---|---|---|---|---|---|---|---|
| Diphtheria | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | 0 |
| Dysentery | 0 | 0 | 1 | 0 | | 1 | 0 | | | |
| Encephalitis, acute | | 1 | | | 0 | | 0 | | | 0 |
| Enteric fever | 0 | 0 | 0 | 0 | | 0 | 0 | | | |
| Infective enteritis or diarrhoea under 2 years | 6 | 1 | 3 | 1 | 0 | 4 | 1 | 2 | | 0 |
| Influenza | 11 | 1 | 1 | 0 | 1 | 8 | 0 | 1 | | 1 |
| Measles | | 0 | 0 | 0 | 0 | | 0 | | | 0 |
| Meningococcal infection | | 1 | 2 | | | | 0 | 2 | | |
| Pneumonia | 237 | 31 | 28 | 9 | 5 | 176 | 29 | | | 3 |
| Poliomyelitis, acute | 3 | 0 | | | 0 | 4 | 0 | | | 0 |
| Scarlet fever | | 0 | 0 | 0 | 0 | | 0 | | | 0 |
| Tuberculosis: Respiratory | 87 | 10 | 16 | 1 | 6 | 108 | 20 | 10 | | 4 |
| Tuberculosis: Non-respiratory | | 0 | 1 | 2 | 1 | | 1 | 1 | | 1 |
| Whooping-cough | 3 | 0 | 1 | 0 | 0 | 0 | 0 | | | 0 |
| Deaths 0–1 year | 215 | 28 | 29 | 9 | 25 | 218 | 32 | 38 | | 6 |
| Deaths (excluding stillbirths) | 5,165 | 728 | 561 | 88 | 187 | 4,975 | 747 | 513 | | 137 |
| LIVE BIRTHS | 6,918 | 1036 | 814 | 210 | 321 | 6,827 | 1060 | 766 | | 346 |
| STILLBIRTHS | 182 | 21 | 18 | | | 183 | 23 | 20 | | |

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

# Vital Statistics

### Infectious Diseases

Only small variations occurred in the trends of infectious diseases in England and Wales during the week ending November 21. The largest were increases in the number of notifications by 213 for scarlet fever, from 1,400 to 1,613, and 100 for whooping-cough, from 2,410 to 2,510.

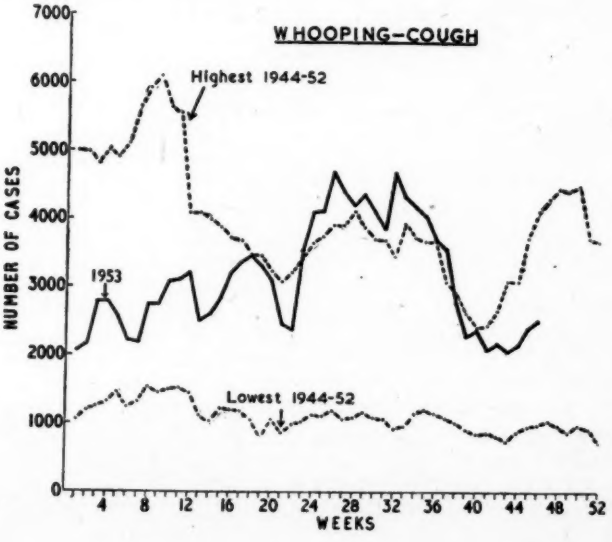
A small rise in the incidence of scarlet fever was recorded in the midland and northern section of the country, while in the area of London, the south-east, and the south-west counties the notifications were 12 fewer than in the preceding week. The largest rise in scarlet fever was 38 in Essex, from 61 to 99. The largest rises in the notifications of whooping-cough were 45 in Staffordshire, from 76 to 121, and 37 in Essex, from 116 to 153, and the largest fall was 33 in Yorkshire West Riding, from 271 to 238. 793 cases of measles were notified, being 23 fewer than in the preceding week. The largest variation in the local trends was a fall of 38 in Staffordshire, from 122 to 84. 28 cases of diphtheria, 2 more than in the previous week, were notified. The chief features of the local returns were a rise in Warwickshire from 0 to 7, all the cases being notified in Birmingham C.B., and a fall in Staffordshire from 13 to 6; 4 of these cases were notified in Coseley U.D. 7 of the 9 cases of paratyphoid fever were notified in Lincolnshire (Louth R.D. 6 and Skegness U.D. 1).

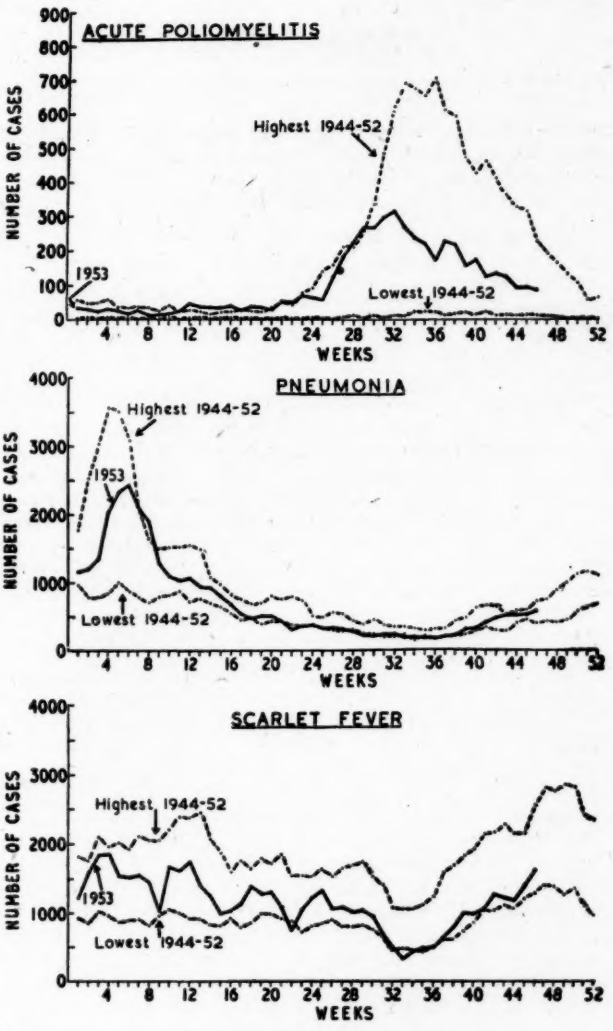
88 cases of acute poliomyelitis were notified. These were 12 fewer for paralytic and 5 more for non-paralytic cases than in the preceding week. The largest returns were Lancashire 11 (Blackpool C.B. 3), Yorkshire West Riding 9, and London 7 (Lewisham 4).

362 cases of dysentery were notified, being 8 fewer than in the preceding week. The largest returns were Yorkshire West Riding 88 (Bradford C.B. 39, Huddersfield C.B. 15, Leeds C.B. 12, Shipley U.D. 10), London 61 (Islington 10 and the remainder scattered through 19 boroughs), Lancashire 48 (Bolton C.B. 11), Middlesex 22 (Willesden M.B. 14), Norfolk 17 (Norwich C.B. 17), and Warwickshire 17 (Birmingham C.B. 15).

### Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1944–52 are shown thus - - - - - - -, the figures for 1953 thus ————. Except for the curves showing notifications in 1953, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.




### Week Ending November 28

The notifications of infectious diseases in England and Wales during the week included scarlet fever 1,484, whooping-cough 2,608, diphtheria 16, measles 875, dysentery 399, acute poliomyelitis 77, paratyphoid fever 3, and typhoid fever 2.

# The Services

A *Supplement* to the *London Gazette* has announced the following awards:

*Third Clasp to the Territorial Efficiency Decoration.*—Lieutenant-Colonel W. J. McIntosh, O.B.E., T.D., R.A.M.C., T.A.

*Second Clasp to the Territorial Efficiency Decoration.*—Lieutenant-Colonel W. J. McIntosh, O.B.E., T.D., Major (acting Lieutenant-Colonel) H. B. Lee, T.D., and Major J. L. Swanston, R.A.M.C., T.A.

*First Clasp to the Territorial Efficiency Decoration.*—Lieutenant-Colonels W. J. McIntosh, O.B.E., T.D., and N. Pyecroft, M.C., T.D., and Majors J. G. Oliver, T.D., J. L. Swanston, and O. T. Wade, R.A.M.C., T.A.

*Territorial Efficiency Decoration.*—Major (Honorary Lieutenant-Colonel) A. J. Webster (now A.E.R.), Majors S. A. Bower, M. N. S. Duncan, J. L. Swanston, C. H. Tonge, and O. T. Wade, Captain (Honorary Major) I. C. K. Mackenzie, and Captain L. S. Bain, R.A.M.C., T.A.

Colonel G. T. L. Archer, late R.A.M.C., has been appointed Honorary Surgeon to the Queen in succession to Major-General F. K. Escritt, C.B., O.B.E., late R.A.M.C., retired.

Captain P. Cuff, R.A.M.C., T.A., has been awarded the Queen's Commendation for brave conduct at Salthouse Heath, Norfolk, on August 12, 1953.

# Medical News

**P.R.C.P.Ed.**—Professor L. S. P. Davidson, professor of medicine at Edinburgh University, has been elected president of the Royal College of Physicians of Edinburgh in succession to Dr. W. A. Alexander.

**Clinical Research Board.**—The names of the members of the new Clinical Research Board have now been announced by the Medical Research Council, after consultation with the Ministry of Health and the Department of Health for Scotland. The establishment of the Board was one of the principal recommendations in the White Paper on "Clinical Research in Relation to the National Health Service" (see *Journal*, July 18, p. 147). The Board has been appointed for three years, with the following membership:—*Chairman:* Sir Geoffrey Jefferson; *Members:* Professor Dugald Baird, Sir Henry Cohen, Professor E. C. Dodds, Sir James Learmonth, Professor A. J. Lewis, Professor G. W. Pickering, Professor R. Platt, Sir James Paterson Ross, Sir James Spence, and Professor B. W. Windeyer; *Assessors:* The Chief Medical Officers of the Ministry of Health, the Department of Health for Scotland, and the Ministry of Health and Local Government in Northern Ireland; *Secretary:* Dr. F. J. C. Herrald.

**Beaver Committee on Air Pollution.**—The Beaver Committee was appointed last July to study the causes, effects, and prevention of air pollution. It has now issued an interim report which in addition to a technical survey of the problem includes recommendations for mitigating the worst effects of smog during the coming winter. These are prefaced by the remark: "No measures that will materially change the present position can be put into effect at short notice." The committee advises that smog warnings from the Meteorological Office should be broadcast; industrial smoke control measures should be improved; during fog urban householders should burn smokeless fuels, and other sources of smoke (including motor cars) should be restricted; and, finally, that those particularly vulnerable to the effects of smog—the elderly, the bronchitic, and cardiac patients—should stay indoors or, if they must go out, wear closely fitting gauze masks or mufflers. The Committee indicts smoke, oxides of sulphur, and "possibly other deleterious substances" as the ingredients which turn the relatively harmless white fog into the dangerous and lethal smog. On the whole, rather less than half the smoke over the country comes from domestic chimneys, and about the same amount from industry; but in last year's London smog up to 60% of the smoke is estimated to have come from domestic fires. A note on the Government's reaction to the report is given in our Parliamentary news (p. 1329).

**Heberden Society.**—The annual dinner of the Heberden Society was held on Friday, December 4, at the Royal College of Surgeons, the president, Lord Horder, being in the chair. The toast of the Society was proposed by Sir David Maxwell Fyfe, who said that they were assembled to do honour to a great physician of the past, the Heberden Society, and one of the great physicians of the day, their retiring president. Heberden was above all a good doctor who cared for his patients, but it was interesting to him to discover that Heberden had had a great influence on the criminologist, for he had disproved the old stories about the mysterious poisons used by people like the Borgias. Heberden's powers of shrewd observation and ruthless criticism were perhaps as necessary to-day when new things like cortisone were in the air. Finally he paid a tribute to the retiring president, Lord Horder, whom he described as "this sprightly young man." In response Lord Horder said that the results of Sir David's researches into their founder would probably be new to many of those present. Lord Horder quoted the observation of Ruskin that "many men talk, some think, and a few observe." Heberden observed. The membership of the Society was limited to one hundred, Lord Horder continued, and there was a long waiting-list. He then presented the Heberden Medal to Sir Russell Brain, who had previously given the Heberden Oration. Miss Patricia Hornsby-Smith, the Parliamentary Secretary to the Ministry of Health, entertained those present with her witty response to the toast of the guests, which had been proposed by Dr. W. S. C. Copeman.

**Linear Accelerator for St. Bartholomew's Hospital.**—A 15-million volt linear accelerator is to be installed in the radiotherapy department of St. Bartholomew's Hospital, London. The machine produces penetrating $x$ rays as a result of the bombardment of platinum foil by electrons. Whereas the $x$ rays from a cobalt bomb are at a potential of 1.3 million volts, those from the linear accelerator will be at 15 million volts. This higher potential results in greater penetration, so that the apparatus is particularly suited to the treatment of deep-seated tumours. A similar machine is being built at Harwell for physical research, but the one at Bart's is claimed to be "the most powerful machine for $x$-ray therapy at the present time." Apart from routine treatment, the linear accelerator will be used for the development of new methods of treatment and for other research. The cost of the apparatus is being met from the hospital's endowment funds. King Edward's Hospital Fund for London is also contributing.

**Multiple Sclerosis Society.**—The Minister of Health, Mr. Iain Macleod, attended the inaugural meeting of the Multiple Sclerosis Society at Chelsea Town Hall, London, on December 2. The Society has been formed by a group of laymen, most of whom have near relatives suffering from the disease. Its declared objects are to encourage research into the cause and cure of multiple sclerosis, to bring interest and hopefulness into the lives of those with the disease, and to develop a rehabilitation programme for them. The society has the advice of an authoritative medical committee.

**Influenza Vaccine.**—American troops in Europe, the Far East, and Alaska are being immunized against influenza this winter, according to a Washington statement.

**Dr. Macdonald Critchley** is one of the three distinguished neurologists to receive the honorary degree of doctor of medicine of Zurich University. The university has been celebrating the centenary of von Monakow's birth, whose classical studies of the visual and acoustic pathways laid the foundation for later work on cerebral localization.

**Sir Lionel Whitby,** Regius Professor of Physic and Master of Downing College, Cambridge, has been elected to an honorary fellowship at Lincoln College, Oxford.

**Mr. Patrick Clarkson** has been invited by the American Society for Hand Surgery to be their guest speaker at its annual meeting in January in Chicago and Cleveland.

**Dr. W. M. Edgar** is to be medical officer to the Daily Mail Himalayan Expedition. The object of the expedition is to find an explanation for the abominable snowman.

## COMING EVENTS

**A World Congress of Catholic Doctors** will be held in Dublin from June 30 to July 4, 1954. The medical and moral aspects of world population trends will be discussed. Further information may be obtained from the secretariate, Veritas House, 7, Lower Abbey Street, Dublin.

**European Society of Cardiovascular Surgery.**—The Society will meet in Edinburgh on July 9 and 10, 1954. The subject to be discussed is "Chronic Oedemas of the Extremities, with the Exception of those Due to Acute Phlebitis." The local secretary is Mr. A. J. Slessor, F.R.C.S., Department of Surgery, University New Buildings, Edinburgh, 8.

**The 14th British Congress of Obstetrics and Gynaecology** will be held at Oxford from July 27 to 30, 1955. All communications relating to the Congress should be sent to the secretary, 14th British Congress of Obstetrics and Gynaecology, Maternity Department, Radcliffe Infirmary, Oxford.

## SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Applications should be made first to the institution concerned.

### Monday, December 14

MEDICAL SOCIETY OF LONDON.—8.30 p.m., Mr. John Bunyan, L.D.S., F.R.M.S.: Short History of the Application of the Microscope to Medicine, Illustrated by Microscopes in the Society's Collection; Dr. G. D. Lumb: Series of Slides and Photographs Illustrating the Pathology and Spread of Cancer of the Breast; Dr. W. H. McMenemey: Slides and Photographs Illustrating the Degenerative Changes in the Brain Following Stoppage of the Heart During Surgical Operation.

●POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. B. G. C. Ackner: Emotional Factors in Treatment Response.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Kettle Memorial Lecture by Professor Geoffrey Hadfield: Dormant Cancer Cell.

ROYAL EYE HOSPITAL.—5.15 p.m., Dr. T. H. Whittington: Accommodation Clinically Considered. Cycloplegics. Retinoscopy.

UNIVERSITY COLLEGE, LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, 4.45 p.m., Public Lecture by Dr. H. Gutfreund: Molecular Forces in Protein Solutions—(II) The Subunit Structure of Crystalline Proteins in Solution.

### Tuesday, December 15

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. F. R. Bettley: Atopy.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—3.45 p.m., Imperial Cancer Research Fund Lecture by Dr. C. le Q. Darcel: Comparative Pathology of Leukotic Conditions in Man and Fowl. 5 p.m., Hunterian Lecture by Professor D Innes Williams: Chronically Dilated Ureter.

SOUTH-WEST LONDON MEDICAL SOCIETY.—At Bolingbroke Hospital, 8.30 p.m., Mr. W. Bentley Purchase: My Experiences as Coroner and Barrister.

WEST END HOSPITAL FOR NERVOUS DISEASES.—5.30 p.m., Dr. T. Rowland Hill: Neurological demonstration.

### Wednesday, December 16

EUGENICS SOCIETY.—At Royal Society, 5.30 p.m., Dr. H. Lehmann: Distribution of the Sickle Cell Trait in Africans and Indian Aboriginals.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. O. Oliver: Laboratory Diagnosis of Syphilis.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. A. H. Harkness: Non-gonococcal Urethritis.

ROYAL EYE HOSPITAL.—5.30 p.m., Mr. H. B. Jacobs: Relation of Nasal and Ocular Diseases.

ROYAL MICROSCOPICAL SOCIETY.—5.30 p.m., Dr. R. W. G. Wyckoff: Electron Microscopy of Viruses.

### Thursday, December 17

EDINBURGH CLINICAL CLUB.—At 7, Drumsheugh Gardens, 8 p.m., Dr. A. G. McGregor: Diagnosis and Treatment of Thyrotoxicosis, with Special Reference to the Use of Radioactive Iodine.

HARVEIAN SOCIETY OF LONDON.—8.15 p.m., Professor Alan Moncrieff: Marasmus; Dr. R. E. Bonham-Carter: Congenital Heart Disease; Dr. B. E. Schlesinger: Infantile Diarrhoea.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5 p.m., Professor F. C. Ormerod: Anatomy of the Paranasal Sinuses.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—3.45 p.m., Erasmus Wilson Demonstration by Dr. J. Stretton Young: Benign Mammary Epithelial Hyperplasia.

### Friday, December 18

INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. F. R. Bettley.

KENT AND CANTERBURY HOSPITAL, Canterbury.—8 p.m., clinical meeting.

ROYAL EYE HOSPITAL.—5.30 p.m., Professor C. A. Keele: Local Anaesthetics in Ophthalmology

●SOCIETY OF CHEMICAL INDUSTRY: FINE CHEMICALS GROUP.—At King's College, Strand, W.C., 7 p.m., Professor D. H. R. Barton: Steroidal Alkaloids.

## BIRTHS, MARRIAGES, AND DEATHS

### BIRTHS

**Kustow.**—On November 13, 1953, at Nuffield House, Guy's Hospital, London, S.E., to Ann, wife of Bernard Kustow, M.B., B.S., a daughter—Miriam.

**Smith.**—On November 18, 1953, at Manchester, to Medora (formerly Storkey), M.B., Ch.B., wife of John Anthony McCredie Smith, M.D., M.R.C.O.G., a daughter.

**Stafford.**—On November 12, 1953, to Eve (formerly Gorringe), wife of William E. Stafford, M.B., B.Ch., of Sion Mills, Co. Tyrone, Northern Ireland, a daughter.

### DEATHS

**Cheesman.**—On November 9, 1953, Herbert Hilton Cheesman, M.R.C.S., L.R.C.P., of Clevedon, Papakura, New Zealand, aged 79.

**Cooper.**—On November 24, 1953, at Budleigh Salterton, Devon, George Cooper, M.D., D.M.R.E.

**Finlay.**—On November 28, 1953, at the Royal Infirmary, Edinburgh, Thomas Yule Finlay, M.D., F.R.C.P.Ed., of 9, Hermitage Gardens, Edinburgh.

**Hosford.**—On September 22, 1953, John Percival Hosford, M.B., B.Ch., of Poole Farm, Bridford, Exeter, Devon, formerly of Bath, Somerset.

**Johnston.**—On November 24, 1953, in a nursing-home, Birkenhead, Donald John Gair Johnston, M.B., Ch.B., D.P.H., of 2, Devonshire Place, Birkenhead, Cheshire.

**Mayer.**—On November 26, 1953, at Bexhill-on-Sea, Sussex, Thomas Frederick Gisborne Mayer, M.R.C.S., L.R.C.P.

**Sainmont.**—On November 14, 1953, Georges Emile Sainmont, M.D., of Ivy Cottage, Leigh Hill, Leigh-on-Sea, Essex, late of 76, Wimpole Street, London, W.

**Scott.**—On November 15, 1953, at 15, Blandford Street, London, W., John Barron Scott, M.B., C.M., formerly of 5, Upper Harley Street, London, W., aged 86.

**Stanley.**—On November 26, 1953, at Sidmouth, Devon, Gilbert Llewellyn Stanley, L.R.C.P.&S.Ed., L.R.F.P.S., aged 64.

**Walker.**—On November 26, 1953, at 50, St. John's Road, Clifton, Bristol, Theodosia Caroline Walker, M.D., aged 81.

**Weston.**—On November 21, 1953, at Singapore, Jean Maryon Weston (formerly Smith), M.B., B.Chir.

# Any Questions?

*Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.*

### Quarantine for Rubella

**Q.**—*I was taught that the quarantine period for rubella should be 21 days, and that patients might remain infective for 7 days after the temperature had fallen. What is the modern view, particularly in regard to pregnant women, examination candidates, and others for whom infection might be a serious matter?*

**A.**—The present-day attitude about rubella must surely be to encourage exposure to infection in childhood and adolescence so that as high a proportion as possible of young women have been infected before marriageable age. The old quarantine of 21 days is therefore not recommended, and the isolation period of 7 days from the onset of rash is not commonly observed. Unfortunately patients are almost certainly infectious during the prodromal period of approximately 24 hours before the rash appears (and for a few days afterwards) so that prompt diagnosis and isolation will not protect the susceptible contact. The only specific protective measure would be to inject the exposed individual with gamma globulin prepared from convalescent cases of rubella, but there is no such material available in this country. As rubella is a mild infection, there would be no point in trying to protect examination candidates, for whom, presumably, arrangements can be made to take a separate examination a few days later. In Australia artificial infection of women students and others gathered together in camps has been recommended.

### Staining of the Teeth by Iron

**Q.**—*A woman who has been taking iron-containing tablets has developed intense staining of her teeth and dentures. What causes this, and how can it be removed?*

**A.**—The patient has been sucking the sugar-coated iron tablets. She should be instructed in future to swallow them whole. Simple brushing does not clean the iron-stained teeth satisfactorily, and this should be done by a dentist using pumice paste. Artificial teeth, if made of acrylic resin, can be soaked in a bleaching solution and carefully rinsed before use; vulcanite dentures, however, are damaged by bleaching and should be cleaned by a dentist.

### Medical Examinations at School

**Q.**—*Does the headteacher or any other member of the teaching staff have any authority to insist on being present with the school medical officer during routine medical examinations at school?*

**A.**—The presence of teachers at medical inspection is discussed fully on pp. 75 and 76 of the *Report of the Chief Medical Officer of the Ministry of Education for the Years 1946 and 1947.*

School medical officers are agreed on the value of a full consultation with both the parent and the teacher. Indeed, one branch of the Society of Medical Officers of Health passed a resolution to the effect that "the medical inspection of schoolchildren should take place in school hours, on school premises, in the presence of parent and teacher." In the report referred to above there is the following comment on this suggestion. "Judging by information reaching the Ministry from time to time, it is evident that this practice does not commend itself to all school medical officers. It has been asked, for example, whether a headteacher, in the face of the examining medical officer's objection, has the right to insist on a member of his or her staff

being allowed to be present at medical inspection. In support of such a claim it is argued that it is of the highest importance that full information regarding a child's physical and mental condition should be available to the class teacher. It is, however, possible for a teacher to be given all the information which he or she ought to have without being present during the inspection itself. Moreover, whilst the teacher can, and frequently does, give the medical officer or school nurse valuable information about a child, it is quite easy to arrange for this to be done otherwise than during the actual inspection. If a mother is present when the child is being examined, it is natural to assume that she will, in the majority of cases, talk more freely to the medical officer if a teacher is not present. This advantage should be offset against, and will probably be considered to outweigh, any arguments advanced in favour of having the teacher in the medical-inspection room. When deciding on any policy involving the disclosure of medical information or the presence of lay persons at medical inspection, one of the things to be borne in mind is that, whereas prior to the coming into operation of the Education Act, 1944, a parent was perfectly free to refuse to have his child inspected under school medical service arrangements, a penalty can now be imposed on a parent who without reasonable excuse fails to present a child for inspection when required so to do. It is therefore more than ever important that the school medical arrangements should be such as to secure and retain the approval and confidence of the parent."

From this it can be gathered that a lay person other than the parent has no authority to insist on being present at the medical examination, yet, at the same time, good sense on both sides should settle any special difficulties which may arise.

### Inheritance of Gargoylism

**Q.**—*A husband and wife (aged 38 and 31 years respectively) have one child aged 9 who suffers from gargoylism. They are anxious to have another child. What are the chances that they will produce a normal child?*

**A.**—The majority of instances of gargoylism are due to a recessive gene. Sometimes a sex-linked gene is unquestionably involved; but this is probably rare. The most likely—and the worst—chance of any subsequent child of these parents suffering from gargoylism is one in four. In view of the doubt whether all examples of gargoylism are simply inherited, the chance may be somewhat better, but it is impossible to say by how much.

### Fissures in the Tongue

**Q.**—*What is the significance of painless, deep, irregular fissures in the tongue of an elderly man?*

**A.**—The fissures described by the questioner are presumably situated on the dorsal aspect of the anterior part of the tongue and are not confined to a more localized area. This condition is not uncommon in elderly patients, and it is difficult to explain its significance. Such a condition is usually unrelated to gastro-intestinal disorder or syphilis. The possibility of subsequent malignant change cannot be excluded, but the likelihood of this is not great. Biopsy in these cases usually shows a rather atrophic mucosa with some underlying fibrosis. It is important to exclude leukoplakia, and any doubtful area of the tongue should be subjected to biopsy.

### "Stripping" for Varicose Veins

**Q.**—*What place has the operation of "stripping" in the treatment of varicose veins?*

**A.**—It is difficult to say exactly what place the operation of "stripping" has in the treatment of varicose veins, but it is certain that at the present time this type of operation is carried out by only few surgeons. The method was introduced by Keller in 1905, and modifications and special instruments were subsequently described by Mayo and also by Babcock. The method never became a very popular one, because it is a blind type of surgery which tears the branches off the main vein and therefore favours the production of thrombi in the lacerated veins and leads to a considerable reaction in the subcutaneous tissues. For these reasons the operation fell into disfavour and has been replaced by procedures which aim at producing thrombosis of the vessels *in situ* without removing them from their bed and lacerating their branches, or by surgical extirpation through various sites. L. B. Fratkin and H. L. Jackes[1] have recently described their technique for carrying out a "stripping" operation.

REFERENCE

[1] *Canad. med. Ass. J.*, 1951, 65, 367.

### Radar and Infertility

**Q.**—*Does work with radar involve any risk of testicular damage? Two patients, whose marriages are infertile, show respectively complete aspermia and oligospermia (5% motility). Both say that they worked with radar during the war.*

**A.**—So far as the writer knows there is no evidence to suggest that work with radar involves risk of testicular damage.

## NOTES AND COMMENTS

**Antiseptics for Surgical Theatres.**—Mr. J. R. GRIFFITHS (Chief Pharmacist at St. Mary Abbots Hospital, London, W.8) writes: The use of solution of borax and formaldehyde is recommended for the storage of previously sterilized sharp instruments in surgical theatres ("Any Questions?" October 31, p. 1004). This preparation originated as a wartime substitute for alcohol for this purpose and appeared in the *National Formularies* of 1943, 1947, and 1949. It was included in the *British Pharmaceutical Codex*, 1949, but deleted from its 1952 *Addendum*, being replaced in this volume, and in the *National Formulary* of 1952, by solution of sodium benzoate and chlorocresol, carrying the subtitle of "surgical instrument preserving solution" and having the following composition: sodium benzoate 1.5 g.; chlorocresol 0.2 g.; and water to 100 ml. The two drawbacks mentioned in your column—namely, the necessity to rinse the instruments in sterile water before using, and the presence of the irritating vapour of formaldehyde—do not occur with the latter preparation, the clause, "Rinse with sterile water," etc., having been omitted from the directions for use. Further, the *Extra Pharmacopoiea*, 1952, Volume I, states that a resinous deposit is apt to form on the instruments immersed in solution of borax and formaldehyde. It would therefore be interesting to know if your recommendation is based on any evidence that the solution of borax and formaldehyde is superior to the more recent solution of sodium benzoate and chlorocresol in its bacteriostatic, bactericidal, or preserving properties.

OUR EXPERT writes: The solution of borax and formaldehyde has the advantage of being a sterilizing solution—that is, capable of destroying all forms of bacteria—as well as being suitable for the storage of previously sterilized instruments. The formation of a resinous deposit on instruments stored in it is outside the experience of extensive users and perhaps attributable to the use of impure ingredients. The solution of chlorocresol has the single advantage of giving off no irritating vapour: the implied suitability of instruments stored in it for immediate use without rinsing is highly questionable.

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